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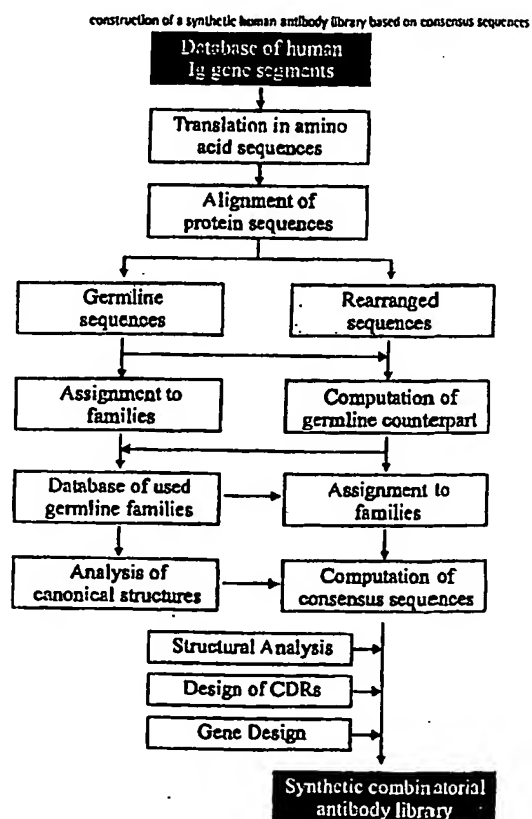
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(54) Title: PROTEIN(POLY)PEPTIDE LIBRARIES

(57) Abstract

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.



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Protein/(Poly)peptide Libraries

Field of the Invention

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.

Background to the Invention

All current recombinant methods which use libraries of proteins/(poly)peptides, e.g. antibodies, to screen for members with desired properties, e.g. binding a given ligand, do not provide the possibility to improve the desired properties of the members in an easy and rapid manner. Usually a library is created either by inserting a random oligonucleotide sequence into one or more DNA sequences cloned from an organism, or a family of DNA sequences is cloned and used as the library. The library is then screened, e.g. using phage display, for members which show the desired property. The sequences of one or more of these resulting molecules are then determined. There is no general procedure available to improve these molecules further on.

Winter (EP 0 368 684 B1) has provided a method for amplifying (by PCR), cloning, and expressing antibody variable region genes. Starting with these genes he was able to create libraries of functional antibody fragments by randomizing the CDR3 of the heavy and/or the light chain. This process is functionally equivalent to the natural process of VJ and VDJ recombination which occurs during the development of B-cells in the immune system.

However the Winter invention does not provide a method for optimizing the binding affinities of antibody fragments further on, a process which would be functionally equivalent to the naturally occurring phenomenon of "affinity maturation", which is provided by the present invention. Furthermore, the Winter invention does not provide for artificial variable region genes, which represent a whole family of

structurally similar natural genes, and which can be assembled from synthetic DNA oligonucleotides. Additionally, Winter does not enable the combinatorial assembly of portions of antibody variable regions, a feature which is provided by the present invention. Furthermore, this approach has the disadvantage that the genes of all antibodies obtained in the screening procedure have to be completely sequenced, since, except for the PCR priming regions, no additional sequence information about the library members is available. This is time and labor intensive and potentially leads to sequencing errors.

The teaching of Winter as well as other approaches have tried to create large antibody libraries having high diversity in the complementarity determining regions (CDRs) as well as in the frameworks to be able to find antibodies against as many different antigens as possible. It has been suggested that a single universal framework may be useful to build antibody libraries, but no approach has yet been successful.

Another problem lies in the production of reagents derived from antibodies. Small antibody fragments show exciting promise for use as therapeutic agents, diagnostic reagents, and for biochemical research. Thus, they are needed in large amounts, and the expression of antibody fragments, e.g. Fv, single-chain Fv (scFv), or Fab in the periplasm of *E. coli* (Skerra & Plückthun, 1988; Better et al., 1988) is now used routinely in many laboratories. Expression yields vary widely, however. While some fragments yield up to several mg of functional, soluble protein per liter and OD of culture broth in shake flask culture (Carter et al., 1992, Plückthun et al. 1996), other fragments may almost exclusively lead to insoluble material, often found in so-called inclusion bodies. Functional protein may be obtained from the latter in modest yields by a laborious and time-consuming refolding process. The factors influencing antibody expression levels are still only poorly understood. Folding efficiency and stability of the antibody fragments, protease lability and toxicity of the expressed proteins to the host cells often severely limit actual production levels, and several attempts have been tried to increase expression yields. For example, Knappik & Plückthun (1995) could show that expression yield depends on the antibody sequence. They identified key residues in the antibody framework which influence expression yields dramatically. Similarly, Ullrich et al. (1995) found that point mutations in the CDRs can increase the yields in periplasmic antibody fragment expression. Nevertheless, these strategies are only applicable to a few antibodies. Since the Winter invention uses existing repertoires of antibodies, no influence on expressibility of the genes is possible.

Furthermore, the findings of Knappik & Plückthun and Ullrich demonstrate that the knowledge about antibodies, especially about folding and expression is still increasing. The Winter invention does not allow to incorporate such improvements into the library design.

The expressibility of the genes is important for the library quality as well, since the screening procedure relies in most cases on the display of the gene product on a phage surface, and efficient display relies on at least moderate expression of the gene.

These disadvantages of the existing methodologies are overcome by the present invention, which is applicable for all collections of homologous proteins. It has the following novel and useful features illustrated in the following by antibodies as an example:

Artificial antibodies and fragments thereof can be constructed based on known antibody sequences, which reflect the structural properties of a whole group of homologous antibody genes. Therefore it is possible to reduce the number of different genes without any loss in the structural repertoire. This approach leads to a limited set of artificial genes, which can be synthesized de novo, thereby allowing introduction of cleavage sites and removing unwanted cleavage sites. Furthermore, this approach enables (i), adapting the codon usage of the genes to that of highly expressed genes in any desired host cell and (ii), analyzing all possible pairs of antibody light (L) and heavy (H) chains in terms of interaction preference, antigen preference or recombinant expression titer, which is virtually impossible using the complete collection of antibody genes of an organism and all combinations thereof.

The use of a limited set of completely synthetic genes makes it possible to create cleavage sites at the boundaries of encoded structural sub-elements. Therefore, each gene is built up from modules which represent structural sub-elements on the protein/(poly)peptide level. In the case of antibodies, the modules consist of "framework" and "CDR" modules. By creating separate framework and CDR modules, different combinatorial assembly possibilities are enabled. Moreover, if two or more artificial genes carry identical pairs of cleavage sites at the boundaries of each of the genetic sub-elements, pre-built libraries of sub-elements can be inserted in these genes simultaneously, without any additional information related to any particular gene sequence. This strategy enables rapid optimization of, for example, antibody affinity, since DNA cassettes encoding libraries of genetic sub-elements can be (i), pre-built, stored and reused and (ii), inserted in any of these

sequences at the right position without knowing the actual sequence or having to determine the sequence of the individual library member.

Additionally, new information about amino acid residues important for binding, stability, or solubility and expression could be integrated into the library design by replacing existing modules with modules modified according to the new observations.

The limited number of consensus sequences used for creating the library allows to speed up the identification of binding antibodies after screening. After having identified the underlying consensus gene sequence, which could be done by sequencing or by using fingerprint restriction sites, just those part(s) comprising the random sequence(s) have to be determined. This reduces the probability of sequencing errors and of false-positive results.

The above mentioned cleavage sites can be used only if they are unique in the vector system where the artificial genes have been inserted. As a result, the vector has to be modified to contain none of these cleavage sites. The construction of a vector consisting of basic elements like resistance gene and origin of replication, where cleavage sites have been removed, is of general interest for many cloning attempts. Additionally, these vector(s) could be part of a kit comprising the above mentioned artificial genes and pre-built libraries.

The collection of artificial genes can be used for a rapid humanization procedure of non-human antibodies, preferably of rodent antibodies. First, the amino acid sequence of the non-human, preferably rodent antibody is compared with the amino acid sequences encoded by the collection of artificial genes to determine the most homologous light and heavy framework regions. These genes are then used for insertion of the genetic sub-elements encoding the CDRs of the non-human, preferably rodent antibody.

Surprisingly, it has been found that with a combination of only one consensus sequence for each of the light and heavy chains of a scFv fragment an antibody repertoire could be created yielding antibodies against virtually every antigen. Therefore, one aspect of the present invention is the use of a single consensus sequence as a universal framework for the creation of useful (poly)peptide libraries and antibody consensus sequences useful therefor.

Detail d D scription of the Invention

The present invention enables the creation of useful libraries of (poly)peptides. In a first embodiment, the invention provides for a method of setting up nucleic acid sequences suitable for the creation of said libraries. In a first step, a collection of at least three homologous proteins is identified and then analyzed. Therefore, a database of the protein sequences is established where the protein sequences are aligned to each other. The database is used to define subgroups of protein sequences which show a high degree of similarity in both the sequence and, if information is available, in the structural arrangement. For each of the subgroups a (poly)peptide sequence comprising at least one consensus sequence is deduced which represents the members of this subgroup; the complete collection of (poly)peptide sequences represent therefore the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is backtranslated into a corresponding coding nucleic acid sequence which is adapted to the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above, is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence or by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic acid sequence and of the sub-elements in the corresponding (poly)peptide.

In a further embodiment, the invention provides for a method which sets up two or more sets of (poly)peptides, where for each set the method as described above is performed, and where the cleavage sites are not only unique within each set but also between any two sets. This method can be applied for the creation of (poly)peptide libraries comprising for example two α -helical domains from two different proteins, where said library is screened for novel hetero-association domains.

In yet a further embodiment, at least two of the sets as described above, are derived from the same collection of proteins or at least a part of it. This describes libraries comprising for example, but not limited to, two domains from antibodies such as VH and VL, or two extracellular loops of transmembrane receptors.

In another embodiment, the nucleic acid sequences set up as described above, are synthesized. This can be achieved by any one of several methods well known to the practitioner skilled in the art, for example, by total gene synthesis or by PCR-based approaches.

In one embodiment, the nucleic acid sequences are cloned into a vector. The vector could be a sequencing vector, an expression vector or a display (e.g. phage display) vector, which are well known to those skilled in the art. Any vector could comprise one nucleic acid sequence, or two or more nucleic sequences, either in different or the same operon. In the last case, they could either be cloned separately or as contiguous sequences.

In one embodiment, the removal of unfavorable interactions as described above, leads to enhanced expression of the modified (poly)peptides.

In a preferred embodiment, one or more sub-sequences of the nucleic acid sequences are replaced by different sequences. This can be achieved by excising the sub-sequences using the conditions suitable for cleaving the cleavage sites adjacent to or at the end of the sub-sequence, for example, by using a restriction enzyme at the corresponding restriction site under the conditions well known to those skilled in the art, and replacing the sub-sequence by a different sequence compatible with the cleaved nucleic acid sequence. In a further preferred embodiment, the different sequences replacing the initial sub-sequence(s) are genomic or rearranged genomic sequences, for example in grafting CDRs from non-human antibodies onto consensus antibody sequences for rapid humanization of non-human antibodies. In the most preferred embodiment, the different sequences are random sequences, thus replacing the sub-sequence by a collection of sequences to introduce variability and to create a library. The random sequences can be assembled in various ways, for example by using a mixture of mononucleotides or preferably a mixture of trinucleotides (Virnekäs et al., 1994) during automated oligonucleotide synthesis, by error-prone PCR or by other methods well known to the practitioner in the art. The random sequences may be completely randomized or biased towards or against certain codons according to

the amino acid distribution at certain positions in known protein sequences. Additionally, the collection of random sub-sequences may comprise different numbers of codons, giving rise to a collection of sub-elements having different lengths.

In another embodiment, the invention provides for the expression of the nucleic acid sequences from a suitable vector and under suitable conditions well known to those skilled in the art.

In a further preferred embodiment, the (poly)peptides expressed from said nucleic acid sequences are screened and, optionally, optimized. Screening may be performed by using one of the methods well known to the practitioner in the art, such as phage-display, selectively infective phage, polysome technology to screen for binding, assay systems for enzymatic activity or protein stability. (Poly)peptides having the desired property can be identified by sequencing of the corresponding nucleic acid sequence or by amino acid sequencing or mass spectrometry. In the case of subsequent optimization, the nucleic acid sequences encoding the initially selected (poly)peptides can optionally be used without sequencing. Optimization is performed by repeating the replacement of sub-sequences by different sequences, preferably by random sequences, and the screening step one or more times.

The desired property the (poly)peptides are screened for is preferably, but not exclusively, selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

In one embodiment, the cleavage sites flanking the sub-sequences are sites recognized and cleaved by restriction enzymes, with recognition and cleavage sequences being either identical or different, the restricted sites either having blunt or sticky ends.

The length of the sub-elements is preferably, but not exclusively ranging between 1 amino acid, such as one residue in the active site of an enzyme or a structure-determining residue, and 150 amino acids, as for whole protein domains. Most preferably, the length ranges between 3 and 25 amino acids, such as most commonly found in CDR loops of antibodies.

The nucleic acid sequences could be RNA or, preferably, DNA.

In one embodiment, the (poly)peptides have an amino acid pattern characteristic of a particular species. This can for example be achieved by deducing the consensus sequences from a collection of homologous proteins of just one species, most preferably from a collection of human proteins. Since the (poly)peptides comprising consensus sequences are artificial, they have to be compared to the protein sequence(s) having the closest similarity to ensure the presence of said characteristic amino acid pattern.

In one embodiment, the invention provides for the creation of libraries of (poly)peptides comprising at least part of members or derivatives of the immunoglobulin superfamily, preferably of member or derivatives of the immunoglobulins. Most preferably, the invention provides for the creation of libraries of human antibodies, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3. In a first step, a database of published antibody sequences of human origin is established where the antibody sequences are aligned to each other. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold of CDR loops (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.

These artificial genes are then constructed e.g. by total gene synthesis or by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the (poly)peptide level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the sub-elements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of corresponding genetic sub-sequences. Most preferably, said (poly)peptides are or are derived from the HuCAL consensus genes: V κ 1, V κ 2, V κ 3, V κ 4, V λ 1, V λ 2, V λ 3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, C κ , C λ , CH1 or any combination of said HuCAL consensus genes.

This collection of DNA molecules can then be used to create libraries of antibodies or antibody fragments, preferably Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments, which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimized using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which

binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. Preferably, an scFv fragment library comprising the combination of HuCAL VH3 and HuCAL VL2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomized as described above.

A further embodiment of the present invention relates to fusion proteins by providing for a DNA sequence which encodes both the (poly)peptide, as described above, as well as an additional moiety. Particularly preferred are moieties which have a useful therapeutic function. For example, the additional moiety may be a toxin molecule which is able to kill cells (Vitetta et al., 1993). There are numerous examples of such toxins, well known to the one skilled in the art, such as the bacterial toxins *Pseudomonas* exotoxin A, and diphtheria toxin, as well as the plant toxins ricin, abrin, modeccin, saporin, and gelonin. By fusing such a toxin for example to an antibody fragment, the toxin can be targeted to, for example, diseased cells, and thereby have a beneficial therapeutic effect. Alternatively, the additional moiety may be a cytokine, such as IL-2 (Rosenberg & Lotze, 1986), which has a particular effect (in this case a T-cell proliferative effect) on a family of cells. In a further embodiment, the additional moiety may confer on its (poly)peptide partner a means of detection and/or purification. For example, the fusion protein could comprise the modified antibody fragment and an enzyme commonly used for detection purposes, such as alkaline phosphatase (Blake et al., 1984). There are numerous other moieties which can be used as detection or purification tags, which are well known to the practitioner skilled in the art. Particularly preferred are peptides comprising at least five histidine residues (Hochuli et al., 1988), which are able to bind to metal ions,

and can therefore be used for the purification of the protein to which they are fused (Lindner et al., 1992). Also provided for by the invention are additional moieties such as the commonly used C-myc and FLAG tags (Hopp et al., 1988; Knappik & Plückthun, 1994).

By engineering one or more fused additional domains, antibody fragments or any other (poly)peptide can be assembled into larger molecules which also fall under the scope of the present invention. For example, mini-antibodies (Pack, 1994) are dimers comprising two antibody fragments, each fused to a self-associating dimerization domain. Dimerization domains which are particularly preferred include those derived from a leucine zipper (Pack & Plückthun, 1992) or helix-turn-helix motif (Pack et al., 1993).

All of the above embodiments of the present invention can be effected using standard techniques of molecular biology known to anyone skilled in the art.

In a further embodiment, the random collection of sub-sequences (the library) is inserted into a singular nucleic acid sequence encoding one (poly)peptide, thus creating a (poly)peptide library based on one universal framework. Preferably a random collection of CDR sub-sequences is inserted into a universal antibody framework, for example into the HuCAL H3k2 single-chain Fv fragment described above.

In further embodiments, the invention provides for nucleic acid sequence(s), vector(s) containing the nucleic acid sequence(s), host cell(s) containing the vector(s), and (poly)peptides, obtainable according to the methods described above.

In a further preferred embodiment, the invention provides for modular vector systems being compatible with the modular nucleic acid sequences encoding the (poly)peptides. The modules of the vectors are flanked by restriction sites unique within the vector system and essentially unique with respect to the restriction sites incorporated into the nucleic acid sequences encoding the (poly)peptides, except for example the restriction sites necessary for cloning the nucleic acid sequences into the vector. The list of vector modules comprises origins of single-stranded replication, origins of double-stranded replication for high- and low copy number plasmids, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, purification and detection tags, and sequences of additional moieties.

The vectors are preferably, but not exclusively, expression vectors or vectors suitable for expression and screening of libraries.

In another embodiment, the invention provides for a kit, comprising one or more of the list of nucleic acid sequence(s), recombinant vector(s), (poly)peptide(s), and vector(s) according to the methods described above, and suitable host cell(s) for producing the (poly)peptide(s).

In a preferred embodiment, the invention provides for the creation of libraries of human antibodies. In a first step, a database of published antibody sequences of human origin is established. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.

These artificial genes are then constructed by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the protein level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the subelements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of said genetic subunits.

This collection of DNA molecules can then be used to create libraries of antibodies which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimised using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDR's) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are eluted, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomised as described above.

Definitions

Protein:

The term protein comprises monomeric polypeptide chains as well as homo- or heteromultimeric complexes of two or more polypeptide chains connected either by covalent interactions (such as disulphide bonds) or by non-covalent interactions (such as hydrophobic or electrostatic interactions).

Analysis of homologous proteins:

The amino acid sequences of three or more proteins are aligned to each other (allowing for introduction of gaps) in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15% of the amino acids in the aligned genes are identical, and at least 30% are similar. Examples for families of homologous proteins are: immunoglobulin superfamily, scavenger receptor superfamily, fibronectin superfamilies (e.g. type II and III), complement control protein superfamily, cytokine receptor superfamily, cystine knot proteins, tyrosine kinases, and numerous other examples well known to one of ordinary skill in the art.

Consensus sequence:

Using a matrix of at least three aligned amino acid sequences, and allowing for gaps in the alignment, it is possible to determine the most frequent amino acid residue at each position. The consensus sequence is that sequence which comprises the amino acids which are most frequently represented at each position. In the event that two or more amino acids are equally represented at a single position, the consensus sequence includes both or all of those amino acids.

Removing unfavorable interactions:

The consensus sequence is per se in most cases artificial and has to be analyzed in order to change amino acid residues which, for example, would prevent the resulting molecule to adapt a functional tertiary structure or which would block the interaction with other (poly)peptide chains in multimeric complexes. This can be done either by (i) building a three-dimensional model of the consensus sequence using known related structures as a template, and identifying amino acid residues within the model which may interact unfavorably with each other, or (ii) analyzing the matrix of aligned amino acid sequences in order to detect combinations of amino

acid residues within the sequences which frequently occur together in one sequence and are therefore likely to interact with each other. These probable interaction-pairs are then tabulated and the consensus is compared with these "interaction maps". Missing or wrong interactions in the consensus are repaired accordingly by introducing appropriate changes in amino acids which minimize unfavorable interactions.

Identification of structural sub-elements:

Structural sub-elements are stretches of amino acid residues within a protein/(poly)peptide which correspond to a defined structural or functional part of the molecule. These can be loops (e.g. CDR loops of an antibody) or any other secondary or functional structure within the protein/(poly)peptide (domains, α -helices, β -sheets, framework regions of antibodies, etc.). A structural sub-element can be identified using known structures of similar or homologous (poly)peptides; or by using the above mentioned matrices of aligned amino acid sequences. Here the variability at each position is the basis for determining stretches of amino acid residues which belong to a structural sub-element (e.g. hypervariable regions of an antibody).

Sub-sequence:

A sub-sequence is defined as a genetic module which is flanked by unique cleavage sites and encodes at least one structural sub-element. It is not necessarily identical to a structural sub-element.

Cleavage site:

A short DNA sequence which is used as a specific target for a reagent which cleaves DNA in a sequence-specific manner (e.g. restriction endonucleases).

Compatible cleavage sites:

Cleavage sites are compatible with each other, if they can be efficiently ligated without modification and, preferably, also without adding an adapter molecule..

Unique cleavage sites:

A cleavage site is defined as unique if it occurs only once in a vector containing at least one of the genes of interest, or if a vector containing at least one of the genes of interest could be treated in a way that only one of the cleavage sites could be used by the cleaving agent.

Corresponding (poly)peptide sequences:

Sequences deduced from the same part of one group of homologous proteins are called corresponding (poly)peptide sequences.

Common cleavage sites:

A cleavage site in at least two corresponding sequences, which occurs at the same functional position (i.e. which flanks a defined sub-sequence), which can be hydrolyzed by the same cleavage tool and which yields identical compatible ends is termed a common cleavage site.

Excising genetic sub-sequences:

A method which uses the unique cleavage sites and the corresponding cleavage reagents to cleave the target DNA at the specified positions in order to isolate, remove or replace the genetic sub-sequence flanked by these unique cleavage sites.

Exchanging genetic sub-sequences:

A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or a collection of sub-sequences, which contain ends compatible with the cleavage sites thus created, is inserted.

Expression of genes:

The term expression refers to in vivo or in vitro processes, by which the information of a gene is transcribed into mRNA and then translated into a protein/(poly)peptide. Thus, the term expression refers to a process which occurs inside cells, by which the information of a gene is transcribed into mRNA and then into a protein. The term expression also includes all events of post-translational modification and transport, which are necessary for the (poly)peptide to be functional.

Screening of protein/(poly)peptide libraries:

Any method which allows isolation of one or more proteins/(poly)peptides having a desired property from other proteins/(poly)peptides within a library.

Amino acid pattern characteristic for a species:

A (poly)peptide sequence is assumed to exhibit an amino acid pattern characteristic for a species if it is deduced from a collection of homologous proteins from just this species.

Immunoglobulin superfamily (IgSF):

The IgSF is a family of proteins comprising domains being characterized by the immunoglobulin fold. The IgSF comprises for example T-cell receptors and the immunoglobulins (antibodies).

Antibody framework:

A framework of an antibody variable domain is defined by Kabat et al. (1991) as the part of the variable domain which serves as a scaffold for the antigen binding loops of this variable domain.

Antibody CDR:

The CDRs (complementarity determining regions) of an antibody consist of the antigen binding loops, as defined by Kabat et al. (1991). Each of the two variable domains of an antibody Fv fragment contain three CDRs.

HuCAL:

Acronym for Human Combinatorial Antibody Library. Antibody Library based on modular consensus genes according to the invention (see Example 1).

Antibody fragment:

Any portion of an antibody which has a particular function, e.g. binding of antigen. Usually, antibody fragments are smaller than whole antibodies. Examples are Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments. Additionally, antibody fragments are often engineered to include new functions or properties.

Universal framework:

One single framework which can be used to create the full variability of functions, specificities or properties which is originally sustained by a large collection of different frameworks, is called universal framework.

Binding of an antibody to its target:

The process which leads to a tight and specific association between an antibody and a corresponding molecule or ligand is called binding. A molecule or ligand or any part of a molecule or ligand which is recognized by an antibody is called the target.

Replacing genetic sub-sequences

A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or collection of sub-

sequences, which contains ends compatible with the cleavage sites thus created, is inserted.

Assembling of genetic sequences:

Any process which is used to combine synthetic or natural genetic sequences in a specific manner in order to get longer genetic sequences which contain at least parts of the used synthetic or natural genetic sequences.

Analysis of homologous genes:

The corresponding amino acid sequences of two or more genes are aligned to each other in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15 per cent of the amino acids in the aligned genes are identical, and at least 30 per cent are similar.

Legends to Figures and Tables

- Fig. 1:** Flow chart outlining the process of construction of a synthetic human antibody library based on consensus sequences.
- Fig. 2:** Alignment of consensus sequences designed for each subgroup (amino acid residues are shown with their standard one-letter abbreviation). (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The positions are numbered according to Kabat (1991). In order to maximize homology in the alignment, gaps (—) have been introduced in the sequence at certain positions.
- Fig. 3:** Gene sequences of the synthetic V kappa consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 4:** Gene sequences of the synthetic V lambda consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 5:** Gene sequences of the synthetic V heavy chain consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 6:** Oligonucleotides used for construction of the consensus genes. The oligos are named according to the corresponding consensus gene, e.g. the gene V κ 1 was constructed using the six oligonucleotides O1K1 to O1K6. The oligonucleotides used for synthesizing the genes encoding the constant domains C κ (OCLK1 to 8) and CH1 (OCH1 to 8) are also shown.
- Fig. 7 A/B:** Sequences of the synthetic genes encoding the constant domains C κ (A) and CH1 (B). The corresponding amino acid sequences as well as unique cleavage sites introduced in these genes are also shown.
- Fig. 7C:** Functional map and sequence of module M24 comprising the synthetic C λ gene segment (huCL lambda).
- Fig. 7D:** Oligonucleotides used for synthesis of module M24.
- Fig. 8:** Sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-V κ 2. The signal sequence (amino acids 1 to 21) was derived from the *E. coli* phoA gene (Skerra &

Plückthun, 1988). Between the *phoA* signal sequence and the VH3 domain, a short sequence stretch encoding 4 amino acid residues (amino acid 22 to 25) has been inserted in order to allow detection of the single-chain fragment in Western blot or ELISA using the monoclonal antibody M1 (Knappik & Plückthun, 1994). The last 6 basepairs of the sequence were introduced for cloning purposes (EcoRI site).

- Fig. 9:** Plasmid map of the vector pLG10.3 used for phage display of the H3k2 scFv fragment. The vector is derived from pLG10 and contains the gene for the *lac* operon repressor, *lacI*, the artificial operon encoding the H3k2-gene3ss fusion under control of the *lac* promoter, the *lpp* terminator of transcription, the single-strand replication origin of the *E. coli* phage f1 (F1_ORI), a gene encoding β -lactamase (*bla*) and the ColEI derived origin of replication.
- Fig. 10:** Sequencing results of independent clones from the initial library, translated into the corresponding amino acid sequences. (A) Amino acid sequence of the VH3 consensus heavy chain CDR3 (position 93 to 102, Kabat numbering). (B) Amino acid sequences of 12 clones of the 10-mer library. (C) Amino acid sequences of 11 clones of the 15-mer library, *: single base deletion.
- Fig. 11:** Expression test of individual library members. (A) Expression of 9 independent clones of the 10-mer library. (B) Expression of 9 independent clones of the 15-mer library. The lane designated with M contains the size marker. Both the gp3-scFv fusion and the scFv monomer are indicated.
- Fig. 12:** Enrichment of specific phage antibodies during the panning against FITC-BSA. The initial as well as the subsequent fluorescein-specific sub-libraries were panned against the blocking buffer and the ratio of the phage eluted from the FITC-BSA coated well vs. that from the powder milk coated well from each panning round is presented as the „specificity factor“.
- Fig. 13:** Phage ELISA of 24 independent clones after the third round of panning tested for binding on FITC-BSA.
- Fig. 14:** Competition ELISA of selected FITC-BSA binding clones. The ELISA signals (OD_{405nm}) of scFv binding without inhibition are taken as 100%.
- Fig. 15:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against FITC-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).

- Fig. 16:** Coomassie-Blue stained SDS-PAGE of the purified anti-fluorescein scFv fragments: M: molecular weight marker, A: total soluble cell extract after induction, B: fraction of the flow-through, C, D and E: purified scFv fragments 1HA-3E4, 1HA-3E5 and 1HA-3E10, respectively.
- Fig. 17:** Enrichment of specific phage antibodies during the panning against β -estradiol-BSA, testosterone-BSA, BSA, ESL-1, interleukin-2, lymphotoxin- β , and LeY-BSA after three rounds of panning.
- Fig. 18:** ELISA of selected ESL-1 and β -estradiol binding clones
- Fig. 19:** Selectivity and cross-reactivity of HuCAL antibodies: in the diagonal specific binding of HuCAL antibodies can be seen, off-diagonal signals show non-specific cross-reactivity.
- Fig. 20:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against β -estradiol-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone is derived from the 10mer library.
- Fig. 21:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against testosterone-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).
- Fig. 22:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against lymphotoxin- β , translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone comprises a 14mer CDR, presumably introduced by incomplete coupling of the trinucleotide mixture during oligonucleotide synthesis.
- Fig. 23:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against ESL-1, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). Two clones are derived from the 10mer library. One clone comprises a 16mer CDR, presumably introduced by chain elongation during oligonucleotide synthesis using trinucleotides.
- Fig. 24:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).
- Fig. 25:** Schematic representation of the modular pCAL vector system.
- Fig. 25a:** List of restriction sites already used in or suitable for the modular HuCAL genes and pCAL vector system.
- Fig. 26:** List of the modular vector elements for the pCAL vector series: shown are only those restriction sites which are part of the modular system.

- Fig. 27:** Functional map and sequence of the multi-cloning site module (MCS)
- Fig. 28:** Functional map and sequence of the pMCS cloning vector series.
- Fig. 29:** Functional map and sequence of the pCAL module M1 (see Fig. 26).
- Fig. 30:** Functional map and sequence of the pCAL module M7-III (see Fig. 26).
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- Fig. 32:** Functional map and sequence of the pCAL module M11-II (see Fig. 26).
- Fig. 33:** Functional map and sequence of the pCAL module M14-Ext2 (see Fig. 26).
- Fig. 34:** Functional map and sequence of the pCAL module M17 (see Fig. 26).
- Fig. 35:** Functional map and sequence of the modular vector pCAL4.
- Fig. 35a:** Functional maps and sequences of additional pCAL modules (M2, M3, M7I, M7II, M8, M10II, M11II, M12, M13, M19, M20, M21, M41) and of low-copy number plasmid vectors (pCALO1 to pCALO3).
- Fig. 35b:** List of oligonucleotides and primers used for synthesis of pCAL vector modules.
- Fig. 36:** Functional map and sequence of the β -lactamase cassette for replacement of CDRs for CDR library cloning.
- Fig. 37:** Oligo and primer design for V κ CDR3 libraries
- Fig. 38:** Oligo and primer design for V λ CDR3 libraries
- Fig. 39:** Functional map of the pBS13 expression vector series.
- Fig. 40:** Expression of all 49 HuCAL scFvs obtained by combining each of the 7 VH genes with each of the 7 VL genes (pBS13, 30°C): Values are given for the percentage of soluble vs. insoluble material, the total and the soluble amount compared to the combination H3 κ 2, which was set to 100%. In addition, the corresponding values for the McPC603 scFv are given.
- Table 1:** Summary of human immunoglobulin germline sequences used for computing the germline membership of rearranged sequences. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. (1) The germline name used in the various calculations, (2) the references number for the corresponding sequence (see appendix for sequence related citations), (3) the family where each sequence belongs to and (4), the various names found in literature for germline genes with identical amino acid sequences.
- Table 2:** Rearranged human sequences used for the calculation of consensus sequences. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The table summarized the name of the sequence (1),

the length of the sequence in amino acids (2), the germline family (3) as well as the computed germline counterpart (4). The number of amino acid exchanges between the rearranged sequence and the germline sequence is tabulated in (5), and the percentage of different amino acids is given in (6). Column (7) gives the references number for the corresponding sequence (see appendix for sequence related citations).

Table 3: Assignment of rearranged V sequences to their germline counterparts. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The germline genes are tabulated according to their family (1), and the number of rearranged genes found for every germline gene is given in (2).

Table 4: Computation of the consensus sequence of the rearranged V kappa sequences. (A), V kappa subgroup 1, (B), V kappa subgroup 2, (C), V kappa subgroup 3 and (D), V kappa subgroup 4. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. (1) Amino acids are given with their standard one-letter abbreviations (and B means D or N, Z means E or Q and X means any amino acid). The statistical analysis summarizes the number of sequences found at each position (2), the number of occurrences of the most common amino acid (3), the amino acid residue which is most common at this position (4), the relative frequency of the occurrence of the most common amino acid (5) and the number of different amino acids found at each position (6).

Table 5: Computation of the consensus sequence of the rearranged V lambda sequences. (A), V lambda subgroup 1, (B), V lambda subgroup 2, and (C), V lambda subgroup 3. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

Table 6: Computation of the consensus sequence of the rearranged V heavy chain sequences. (A), V heavy chain subgroup 1A, (B), V heavy chain subgroup 1B, (C), V heavy chain subgroup 2, (D), V heavy chain subgroup 3, (E), V heavy chain subgroup 4, (F), V heavy chain subgroup 5, and (G), V heavy chain subgroup 6. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

Examples

Example 1: Design of a Synthetic Human Combinatorial Antibody Library (HuCAL)

The following example describes the design of a fully synthetic human combinatorial antibody library (HuCAL), based on consensus sequences of the human immunoglobulin repertoire, and the synthesis of the consensus genes. The general procedure is outlined in Fig. 1.

1.1 Sequence database

1.1.1 Collection and alignment of human immunoglobulin sequences

In a first step, sequences of variable domains of human immunoglobulins have been collected and divided into three sub bases: V heavy chain (VH), V kappa (V κ) and V lambda (V λ). For each sequence, the gene sequence was then translated into the corresponding amino acid sequence. Subsequently, all amino acid sequences were aligned according to Kabat et al. (1991). In the case of V λ sequences, the numbering system of Chuchana et al. (1990) was used. Each of the three main databases was then divided into two further sub bases: the first sub base contained all sequences derived from rearranged V genes, where more than 70 positions of the sequence were known. The second sub base contained all germline gene segments (without the D- and J- minigenes; pseudogenes with internal stop codons were also removed). In all cases, where germline sequences with identical amino acid sequence but different names were found, only one sequence was used (see Table 1). The final databases of rearranged sequences contained 386, 149 and 674 entries for V κ , V λ and VH, respectively. The final databases of germline sequences contained 48, 26 and 141 entries for V κ , V λ and VH, respectively.

1.1.2 Assignment of sequences to subgroups

The sequences in the three germline databases were then grouped according to sequence homology (see also Tomlinson et al., 1992, Williams & Winter, 1993, and Cox et al., 1994). In the case of V κ , 7 families could be established. V λ was divided into 8 families and VH into 6 families. The VH germline genes of the VH7 family (Van Dijk et al., 1993) were grouped into the VH1 family, since the genes of the two families are highly homologous. Each family contained different numbers of germline genes, varying from 1 (for example VH6) to 47 (VH3).

1.2 Analysis of sequences

1.2.1 Computation of germline membership

For each of the 1209 amino acid sequences in the databases of rearranged genes, the nearest germline counterpart, i.e. the germline sequence with the smallest number of amino acid differences was then calculated. After the germline counterpart was found, the number of somatic mutations which occurred in the rearranged gene and which led to amino acid exchanges could be tabulated. In 140 cases, the germline counterpart could not be calculated exactly, because more than one germline gene was found with an identical number of amino acid exchanges. These rearranged sequences were removed from the database. In a few cases, the number of amino acid exchanges was found to be unusually large (>20 for VL and >25 for VH), indicating either heavily mutated rearranged genes or derivation from germline genes not present in the database. Since it was not possible to distinguish between these two possibilities, these sequences were also removed from the database. Finally, 12 rearranged sequences were removed from the database because they were found to have very unusual CDR lengths and composition or unusual amino acids at canonical positions (see below). In summary, 1023 rearranged sequences out of 1209 (85%) could be clearly assigned to their germline counterparts (see Table 2).

After this calculation, every rearranged gene could be arranged in one of the families established for the germline genes. Now the usage of each germline gene, i.e. the number of rearranged genes which originate from each germline gene, could be calculated (see Table 2). It was found that the usage was strongly biased towards a subset of germline genes; whereas most of the germline genes were not present as rearranged genes in the database and therefore apparently not used in the immune system (Table 3). This observation had already been reported in the case of V κ (Cox, et al., 1994). All germline gene families, where no or only very few rearranged counterparts could be assigned, were removed from the database, leaving 4 V κ , 3 V λ , and 6 VH families.

1.2.2 Analysis of CDR conformations

The conformation of the antigen binding loops of antibody molecules, the CDRs, is strongly dependent on both the length of the CDRs and the amino acid residues located at the so-called canonical positions (Chothia & Lesk, 1987). It has been found that only a few canonical structures exist, which determine the structural

repertoire of the immunoglobulin variable domains (Chothia et al., 1989). The canonical amino acid positions can be found in CDR as well as framework regions. The 13 used germline families defined above (7 VL and 6 VH) were now analyzed for their canonical structures in order to define the structural repertoire encoded in these families.

In 3 of the 4 V κ families (V κ 1, 2 and 4), one different type of CDR1 conformation could be defined for every family. The family V κ 3 showed two types of CDR1 conformation: one type which was identical to V κ 1 and one type only found in V κ 3. All V κ CDR2s used the same type of canonical structure. The CDR3 conformation is not encoded in the germline gene segments. Therefore, the 4 V κ families defined by sequence homology and usage corresponded also to 4 types of canonical structures found in V κ germline genes.

The 3 V λ families defined above showed 3 types of CDR1 conformation, each family with one unique type. The V λ 1 family contained 2 different CDR1 lengths (13 and 14 amino acids), but identical canonical residues, and it is thought that both lengths adopt the same canonical conformation (Chothia & Lesk, 1987). In the CDR2 of the used V λ germlines, only one canonical conformation exists, and the CDR3 conformation is not encoded in the germline gene segments. Therefore, the 3 V λ families defined by sequence homology and usage corresponded also to 3 types of canonical structures.

The structural repertoire of the human VH sequences was analyzed in detail by Chothia et al., 1992. In total, 3 conformations of CDR1 (H1-1, H1-2 and H1-3) and 6 conformations of CDR2 (H2-1, H2-2, H2-3, H2-4, H2-5 and H2-x) could be defined. Since the CDR3 is encoded in the D- and J-minigene segments, no particular canonical residues are defined for this CDR.

All the members of the VH1 family defined above contained the CDR1 conformation H1-1, but differed in their CDR2 conformation: the H2-2 conformation was found in 6 germline genes, whereas the conformation H2-3 was found in 8 germline genes. Since the two types of CDR2 conformations are defined by different types of amino acid at the framework position 72, the VH1 family was divided into two subfamilies: VH1A with CDR2 conformation H2-2 and VH1B with the conformation H2-3. The members of the VH2 family all had the conformations H1-3 and H2-1 in CDR1 and CDR2, respectively. The CDR1 conformation of the VH3 members was found in all cases to be H1-1, but 4 different types were found in CDR2 (H2-1, H2-3, H2-4 and H2-x). In these CDR2 conformations, the canonical framework residue 71 is always

defined by an arginine. Therefore, it was not necessary to divide the VH3 family into subfamilies, since the 4 types of CDR2 conformations were defined solely by the CDR2 itself. The same was true for the VH4 family. Here, all 3 types of CDR1 conformations were found, but since the CDR1 conformation was defined by the CDR itself (the canonical framework residue 26 was found to be glycine in all cases), no subdivisions were necessary. The CDR2 conformation of the VH4 members was found to be H2-1 in all cases. All members of the VH5 family were found to have the conformation H1-1 and H2-2, respectively. The single germline gene of the VH6 family had the conformations H1-3 and H2-5 in CDR1 and CDR2, respectively.

In summary, all possible CDR conformations of the V κ and V λ genes were present in the 7 families defined by sequence comparison. From the 12 different CDR conformations found in the used VH germline genes, 7 could be covered by dividing the family VH1 into two subfamilies, thereby creating 7 VH families. The remaining 5 CDR conformations (3 in the VH3 and 2 in the VH4 family) were defined by the CDRs themselves and could be created during the construction of CDR libraries. Therefore, the structural repertoire of the used human V genes could be covered by 49 (7 x 7) different frameworks.

1.2.3 Computation of consensus sequences

The 14 databases of rearranged sequences (4 V κ , 3 V λ and 7 VH) were used to compute the HuCAL consensus sequences of each subgroup (4 HuCAL- V κ , 3 HuCAL- V λ , 7 HuCAL- VH, see Table 4, 5 and 6). This was done by counting the number of amino acid residues used at each position (position variability) and subsequently identifying the amino acid residue most frequently used at each position. By using the rearranged sequences instead of the used germline sequences for the calculation of the consensus, the consensus was weighted according to the frequency of usage. Additionally, frequently mutated and highly conserved positions could be identified. The consensus sequences were cross-checked with the consensus of the germline families to see whether the rearranged sequences were biased at certain positions towards amino acid residues which do not occur in the collected germline sequences, but this was found not to be the case. Subsequently, the number of differences of each of the 14 consensus sequences to each of the germline sequences found in each specific family was calculated. The overall deviation from the most homologous germline sequence was found to be 2.4 amino acid residues (s.d. = 2.7), ensuring that the "artificial" consensus sequences

can still be considered as truly human sequences as far as immunogenicity is concerned.

1.3 Structural analysis

So far, only sequence information was used to design the consensus sequences. Since it was possible that during the calculation certain artificial combinations of amino acid residues have been created, which are located far away in the sequence but have contacts to each other in the three dimensional structure, leading to destabilized or even misfolded frameworks, the 14 consensus sequences were analyzed according to their structural properties.

It was rationalized that all rearranged sequences present in the database correspond to functional and therefore correctly folded antibody molecules. Hence, the most homologous rearranged sequence was calculated for each consensus sequence. The positions where the consensus differed from the rearranged sequence were identified as potential "artificial residues" and inspected.

The inspection itself was done in two directions. First, the local sequence stretch around each potentially "artificial residue" was compared with the corresponding stretch of all the rearranged sequences. If this stretch was found to be truly artificial, i.e. never occurred in any of the rearranged sequences, the critical residue was converted into the second most common amino acid found at this position and analyzed again. Second, the potentially "artificial residues" were analyzed for their long range interactions. This was done by collecting all available structures of human antibody variable domains from the corresponding PDB files and calculating for every structure the number and type of interactions each amino acid residue established to each side-chain. These "interaction maps" were used to analyze the probable side-chain/side-chain interactions of the potentially "artificial residues". As a result of this analysis, the following residues were exchanged (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: S₆₅T

Vκ1: N₃₄A,

Vκ3: G₉A, D₆₀A, R₇₇S

Vλ3: V₇₈T

1.4 Design of CDR sequences

The process described above provided the complete consensus sequences derived solely from the databases of rearranged sequences. It was rationalized that the CDR1 and CDR2 regions should be taken from the databases of used germline sequences, since the CDRs of rearranged and mutated sequences are biased towards their particular antigens. Moreover, the germline CDR sequences are known to allow binding to a variety of antigens in the primary immune response, where only CDR3 is varied. Therefore, the consensus CDRs obtained from the calculations described above were replaced by germline CDRs in the case of VH and V κ . In the case of V λ , a few amino acid exchanges were introduced in some of the chosen germline CDRs in order to avoid possible protease cleavage sites as well as possible structural constraints.

The CDRs of following germline genes have been chosen:

<u>HuCAL gene</u>	<u>CDR1</u>	<u>CDR2</u>
HuCAL-VH1A	VH1-12-1	VH1-12-1
HuCAL-VH1B	VH1-13-16	VH1-13-6,-7,-8,-9
HuCAL-VH2	VH2-31-10,-11,-12,-13	VH2-31-3,-4
HuCAL-VH3	VH3-13-8,-9,-10	VH3-13-8,-9,-10
HuCAL-VH4	VH4-11-7 to -14	VH4-11-8,-9,-11,-12,-14,-16 VH4-31-17,-18,-19,-20
HuCAL-VH5	VH5-12-1,-2	VH5-12-1,-2
HuCAL-VH6	VH6-35-1	VH6-35-1
HuCAL-V κ 1	V κ 1-14,-15	V κ 1-2,-3,-4,-5,-7,-8,-12,-13,-18,-19
HuCAL-V κ 2	V κ 2-6	V κ 2-6
HuCAL-V κ 3	V κ 3-1,-4	V κ 3-4
HuCAL-V κ 4	V κ 4-1	V κ 4-1
HuCAL-V λ 1	HUMLV117,DPL5	DPL5
HuCAL-V λ 2	DPL11,DPL12	DPL12
HuCAL-V λ 3	DPL23	HUMLV318

In the case of the CDR3s, any sequence could be chosen since these CDRs were planned to be the first to be replaced by oligonucleotide libraries. In order to study the expression and folding behavior of the consensus sequences in *E. coli*, it would be useful to have all sequences with the same CDR3, since the influence of the CDR3s on the folding behavior would then be identical in all cases. The dummy sequences QQHYTTPP and ARWGGDGFYAMDY were selected for the VL chains (kappa and lambda) and for the VH chains, respectively. These sequences are known to be compatible with antibody folding in *E. coli* (Carter et al., 1992).

1.5 Gene design

The final outcome of the process described above was a collection of 14 HuCAL amino acid sequences, which represent the frequently used structural antibody repertoire of the human immune system (see Figure 2). These sequences were back-translated into DNA sequences. In a first step, the back-translation was done using only codons which are known to be frequently used in *E. coli*. These gene sequences were then used for creating a database of all possible restriction endonuclease sites, which could be introduced without changing the corresponding amino acid sequences. Using this database, cleavage sites were selected which were located at the flanking regions of all sub-elements of the genes (CDRs and framework regions) and which could be introduced in all HuCAL VH, V κ or V λ genes simultaneously at the same position. In a few cases it was not possible to find cleavage sites for all genes of a subgroup. When this happened, the amino acid sequence was changed, if this was possible according to the available sequence and structural information. This exchange was then analyzed again as described above. In total, the following 6 amino acid residues were exchanged during this design (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: T₃Q

VH6: S₄₂G

V κ 3: E₁D, I₅₆V

V κ 4: K₂₄R

V λ 3: T₂₂S

In one case (5'-end of VH framework 3) it was not possible to identify a single cleavage site for all 7 VH genes. Two different type of cleavage sites were used instead: BstEII for HuCAL VH1A, VH1B, VH4 and VH5, and NspV for HuCAL VH2, VH3, VH4 and VH6.

Several restriction endonuclease sites were identified, which were not located at the flanking regions of the sub-elements but which could be introduced in every gene of a given group without changing the amino acid sequence. These cleavage sites were also introduced in order to make the system more flexible for further improvements. Finally, all but one remaining restriction endonuclease sites were removed in every gene sequence. The single cleavage site, which was not removed was different in all genes of a subgroup and could be therefore used as a "fingerprint" site to ease the identification of the different genes by restriction digest. The designed genes, together with the corresponding amino acid sequences and the group-specific restriction endonuclease sites are shown in Figure 3, 4 and 5, respectively.

1.6 Gene synthesis and cloning

The consensus genes were synthesized using the method described by Prodromou & Pearl, 1992, using the oligonucleotides shown in Fig. 6. Gene segments encoding the human constant domains C κ , C λ and CH1 were also synthesized, based on sequence information given by Kabat et al., 1991 (see Fig. 6 and Fig. 7). Since for both the CDR3 and the framework 4 gene segments identical sequences were chosen in all HuCAL V κ , V λ and VH genes, respectively, this part was constructed only once, together with the corresponding gene segments encoding the constant domains. The PCR products were cloned into pCR-Script KS(+) (Stratagene, Inc.) or pZER0-1 (Invitrogen, Inc.) and verified by sequencing.

Example 2: Cloning and Testing of a HuCAL-Based Antibody Library

A combination of two of the synthetic consensus genes was chosen after construction to test whether binding antibody fragments can be isolated from a library based on these two consensus frameworks. The two genes were cloned as a single-chain Fv (scFv) fragment, and a VH-CDR3 library was inserted. In order to test the library for the presence of functional antibody molecules, a selection procedure

was carried out using the small hapten fluorescein bound to BSA (FITC-BSA) as antigen.

2.1 Cloning of the HuCAL VH3-Vk2 scFv fragment

In order to test the design of the consensus genes, one randomly chosen combination of synthetic light and heavy gene (HuCAL-Vk2 and HuCAL-VH3) was used for the construction of a single-chain antibody (scFv) fragment. Briefly, the gene segments encoding the VH3 consensus gene and the CH1 gene segment including the CDR3 - framework 4 region, as well as the Vk2 consensus gene and the Ck gene segment including the CDR3 - framework 4 region were assembled yielding the gene for the VH3-CH1 Fd fragment and the gene encoding the Vk2-Ck light chain, respectively. The CH1 gene segment was then replaced by an oligonucleotide cassette encoding a 20-mer peptide linker with the sequence AGGGSGGGSGGGSGGGGS. The two oligonucleotides encoding this linker were 5'- TCAGCGGGTGGCGGTTCTGGCGGCGGTGGGAGCGGTGGCGGTGGTTC-TGGCGGTGGTGGTTCGATATCGGTCCACGTACGG-3' and 5'-AATTCCGTACG-TGGACCGATATCGGAACCACCACCGCCAGAACCAGCGCCACCGCTCCCACCGC CGCCAGAACCGCCACCCGC-3', respectively. Finally, the HuCAL-Vk2 gene was inserted *via* EcoRV and BsiWI into the plasmid encoding the HuCAL-VH3-linker fusion, leading to the final gene HuCAL-VH3-Vk2, which encoded the two consensus sequences in the single-chain format VH-linker-VL. The complete coding sequence is shown in Fig. 8.

2.2 Construction of a monovalent phage-display phagemid vector pIG10.3

Phagemid pIG10.3 (Fig. 9) was constructed in order to create a phage-display system (Winter et al., 1994) for the H3k2 scFv gene. Briefly, the EcoRI/HindIII restriction fragment in the phagemid vector pIG10 (Ge et al., 1995) was replaced by the c-myc followed by an amber codon (which encodes an glutamate in the amber-suppressor strain XL1 Blue and a stop codon in the non-suppressor strain JM83) and a truncated version of the gene III (fusion junction at codon 249, see Lowman et al., 1991) through PCR mutagenesis.

2.3 Construction of H-CDR3 libraries

Heavy chain CDR3 libraries of two lengths (10 and 15 amino acids) were constructed using trinucleotide codon containing oligonucleotides (Virnekās et al., 1994) as templates and the oligonucleotides complementing the flanking regions as primers. To concentrate only on the CDR3 structures that appear most often in functional antibodies, we kept the salt-bridge of R_{H94} and D_{H101} in the CDR3 loop. For the 15-mer library, both phenylalanine and methionine were introduced at position 100 since these two residues were found to occur quite often in human CDR3s of this length (not shown). For the same reason, valine and tyrosine were introduced at position 102. All other randomized positions contained codons for all amino acids except cysteine, which was not used in the trinucleotide mixture.

The CDR3 libraries of lengths 10 and 15 were generated from the PCR fragments using oligonucleotide templates O3HCDR103T (5'- GATACGGCCGTGTATTATTGCGCGCGT (TRI)₆GATTATTGGGGCCAAGGCACCCTG-3') and O3HCDR153T (5'-GATACGGCCGT GTATTATTGCGCGCGT(TRI)₁₀(TTT/ATG)GAT(GTT/TAT)TGGGGCCAAGGCACCCTG-3'), and primers O3HCDR35 (5'-GATACGGCCGTGTATTATTGC-3') and O3HCDR33 (5'-CAGGGTGCCTTGGCCCC-3'), where TRI are trinucleotide mixtures representing all amino acids without cysteine, (TTT/ATG) and (GTT/TAT) are trinucleotide mixtures encoding the amino acids phenylalanine/methionine and valine/tyrosine, respectively. The potential diversity of these libraries was 4.7×10^7 and 3.4×10^{10} for 10-mer and 15-mer library, respectively. The library cassettes were first synthesized from PCR amplification of the oligo templates in the presence of both primers: 25 pmol of the oligo template O3HCDR103T or O3HCDR153T, 50 pmol each of the primers O3HCDR35 and O3HCDR33, 20 nmol of dNTP, 10x buffer and 2.5 units of Pfu DNA polymerase (Stratagene) in a total volume of 100 µl for 30 cycles (1 minute at 92°C, 1 minute at 62°C and 1 minute at 72°C). A hot-start procedure was used. The resulting mixtures were phenol-extracted, ethanol-precipitated and digested overnight with EagI and Styl. The vector pIG10.3-sch3k2cat, where the EagI-Styl fragment in the vector pIG10.3-sch3k2 encoding the H-CDR3 was replaced by the chloramphenicol acetyltransferase gene (cat) flanked with these two sites, was similarly digested. The digested vector (35 µg) was gel-purified and ligated with 100 µg of the library cassette overnight at 16°C. The ligation mixtures were isopropanol precipitated, air-dried and the pellets were redissolved in 100 µl of ddH₂O. The ligation was mixed with 1 ml of freshly prepared electrocompetent XL1 Blue on ice. 20 rounds of electroporation were performed and the transformants were diluted in SOC medium, shaken at 37°C for 30 minutes and plated out on large LB plates (Amp/Tet/Glucose)

at 37°C for 6-9 hrs. The number of transformants (library size) was 3.2×10^7 and 2.3×10^7 for the 10-mer and the 15-mer library, respectively. The colonies were suspended in 2xYT medium (Amp/Tet/Glucose) and stored as glycerol culture.

In order to test the quality of the initial library, phagemids from 24 independent colonies (12 from the 10-mer and 12 from the 15-mer library, respectively) were isolated and analyzed by restriction digestion and sequencing. The restriction analysis of the 24 phagemids indicated the presence of intact vector in all cases. Sequence analysis of these clones (see Fig. 10) indicated that 22 out of 24 contained a functional sequence in their heavy chain CDR3 regions. 1 out of 12 clones of the 10-mer library had a CDR3 of length 9 instead of 10, and 2 out of 12 clones of the 15-mer library had no open reading frame, thereby leading to a non-functional scFv; one of these two clones contained two consecutive inserts, but out of frame (data not shown). All codons introduced were presented in an even distribution.

Expression levels of individual library members were also measured. Briefly, 9 clones from each library were grown in 2xYT medium containing Amp/Tet/0.5% glucose at 37°C overnight. Next day, the cultures were diluted into fresh medium with Amp/Tet. At an OD_{600nm} of 0.4, the cultures were induced with 1 mM of IPTG and shaken at RT overnight. Then the cell pellets were suspended in 1 ml of PBS buffer + 1 mM of EDTA. The suspensions were sonicated and the supernatants were separated on an SDS-PAGE under reducing conditions, blotted on nylon membrane and detected with anti-FLAG M1 antibody (see Fig. 11). From the nine clones of the 10-mer library, all express the scFv fragments. Moreover, the gene III / scFv fusion proteins were present in all cases. Among the nine clones from the 15-mer library analyzed, 6/9 (67%) led to the expression of both scFv and the gene III/scFv fusion proteins. More importantly, all clones expressing the scFvs and gene III/scFv fusions gave rise to about the same level of expression.

2.4 Biopanning

Phages displaying the antibody libraries were prepared using standard protocols. Phages derived from the 10-mer library were mixed with phages from the 15-mer library in a ratio of 20:1 (1×10^{10} cfu/well of the 10-mer and 5×10^8 cfu/well of the 15-mer phages, respectively). Subsequently, the phage solution was used for panning in ELISA plates (Maxisorp, Nunc) coated with FITC-BSA (Sigma) at concentration of 100 µg/ml in PBS at 4°C overnight. The antigen-coated wells were blocked with 3% powder milk in PBS and the phage solutions in 1% powder milk were added to each

well and the plate was shaken at RT for 1 hr. The wells were then washed with PBST and PBS (4 times each with shaking at RT for 5 minutes). The bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. The eluted phage solutions were immediately neutralized with 1/2 the volume of 1 M Tris·Cl, pH 7.6. Eluted phage solutions (ca. 450 μ l) were used to infect 5 ml of XL1 Blue cells at 37°C for 30 min. The infected cultures were then plated out on large LB plates (Amp/Tet/Glucose) and allowed to grow at 37°C until the colonies were visible. The colonies were suspended in 2xYT medium and the glycerol cultures were made as above described. This panning round was repeated twice, and in the third round elution was carried out with addition of fluorescein in a concentration of 100 μ g/ml in PBS. The enrichment of specific phage antibodies was monitored by panning the initial as well as the subsequent fluorescein-specific sub-libraries against the blocking buffer (Fig. 12). Antibodies with specificity against fluorescein were isolated after 3 rounds of panning.

2.5 ELISA measurements

One of the criteria for the successful biopanning is the isolation of individual phage clones that bind to the targeted antigen or hapten. We undertook the isolation of anti-FITC phage antibody clones and characterized them first in a phage ELISA format. After the 3rd round of biopanning (see above), 24 phagemid containing clones were used to inoculate 100 μ l of 2xYT medium (Amp/Tet/Glucose) in an ELISA plate (Nunc), which was subsequently shaken at 37°C for 5 hrs. 100 μ l of 2xYT medium (Amp/Tet/1 mM IPTG) were added and shaking was continued for 30 minutes. A further 100 μ l of 2xYT medium (Amp/Tet) containing the helper phage (1×10^9 cfu/well) was added and shaking was done at RT for 3 hrs. After addition of kanamycin to select for successful helper phage infection, the shaking was continued overnight. The plates were then centrifuged and the supernatants were pipetted directly into ELISA wells coated with 100 μ l FITC-BSA (100 μ g/ml) and blocked with milk powder. Washing was performed similarly as during the panning procedure and the bound phages were detected with anti-M13 antibody-POD conjugate (Pharmacia) using soluble POD substrate (Boehringer-Mannheim). Of the 24 clones screened against FITC-BSA, 22 were active in the ELISA (Fig. 13). The initial libraries of similar titer gave rise to no detectable signal. Specificity for fluorescein was measured in a competitive ELISA. Periplasmic fractions of five FITC specific scFvs were prepared as described above. Western blotting indicated that all clones expressed about the same amount of scFv fragment

(data not shown). ELISA was performed as described above, but additionally, the periplasmic fractions were incubated 30 min at RT either with buffer (no inhibition), with 10 mg/ml BSA (inhibition with BSA) or with 10 mg/ml fluorescein (inhibition with fluorescein) before adding to the well. Binding scFv fragment was detected using the anti-FLAG antibody M1. The ELISA signal could only be inhibited, when soluble fluorescein was added, indicating binding of the scFvs was specific for fluorescein (Fig. 14).

2.6 Sequence analysis

The heavy chain CDR3 region of 20 clones were sequenced in order to estimate the sequence diversity of fluorescein binding antibodies in the library (Fig. 15). In total, 16 of 20 sequences (80%) were different, showing that the constructed library contained a highly diverse repertoire of fluorescein binders. The CDR3s showed no particular sequence homology, but contained on average 4 arginine residues. This bias towards arginine in fluorescein binding antibodies had already been described by Barbas et al., 1992.

2.7 Production

E. coli JM83 was transformed with phagemid DNA of 3 selected clones and cultured in 0.5 L 2xYT medium. Induction was carried out with 1 mM IPTG at $OD_{600nm} = 0.4$ and growth was continued with vigorous shaking at RT overnight. The cells were harvested and pellets were suspended in PBS buffer and sonicated. The supernatants were separated from the cell debris via centrifugation and purified via the BioLogic system (Bio-Rad) by with a POROS[®]MC 20 column (IMAC, PerSeptive Biosystems, Inc.) coupled with an ion-exchange chromatography column. The ion-exchange column was one of the POROS[®]HS, CM or HQ or PI 20 (PerSeptive Biosystems, Inc.) depended on the theoretical pI of the scFv being purified. The pH of all the buffers was adjusted to one unit lower or higher than the pI of the scFv being purified throughout. The sample was loaded onto the first IMAC column, washed with 7 column volumes of 20 mM sodium phosphate, 1 M NaCl and 10 mM imidazole. This washing was followed by 7 column volumes of 20 mM sodium phosphate and 10 mM imidazole. Then 3 column volumes of an imidazole gradient (10 to 250 mM) were applied and the eluent was connected directly to the ion-exchanger. Nine column volumes of isocratic washing with 250 mM imidazole was followed by 15 column volumes of 250 mM to 100 mM and 7 column volumes of an imidazole / NaCl gradient (100 to 10 mM imidazole, 0 to 1 M NaCl). The flow rate was 5 ml/min. The purity of scFv fragments was checked by SDS-PAGE Coomassie

staining (Fig. 16). The concentration of the fragments was determined from the absorbance at 280 nm using the theoretically determined extinction coefficient (Gill & von Hippel, 1989). The scFv fragments could be purified to homogeneity (see Fig. 16). The yield of purified fragments ranged from 5 to 10 mg/L/OD.

Example 3: HuCAL H3 κ 2 Library Against a Collection of Antigens

In order to test the library used in Example 2 further, a new selection procedure was carried out using a variety of antigens comprising β -estradiol, testosterone, Lewis-Y epitope (LeY), interleukin-2 (IL-2), lymphotoxin- β (LT- β), E-selectin ligand-1 (ESL-1), and BSA.

3.1 Biopanning

The library and all procedures were identical to those described in Example 2. The ELISA plates were coated with β -estradiol-BSA (100 μ g/ml), testosterone-BSA (100 μ g/ml), LeY-BSA (20 μ g/ml) IL-2 (20 μ g/ml), ESL-1 (20 μ g/ml) and BSA (100 μ g/ml), LT- β (denatured protein, 20 μ g/ml). In the first two rounds, bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. In the case of BSA, elution after three rounds of panning was carried out with addition of BSA in a concentration of 100 μ g/ml in PBS. In the case of the other antigens, third round elution was done with 0.1 M triethylamine. In all cases except LeY, enrichment of binding phages could be seen (Figure 17). Moreover, a repetition of the biopanning experiment using only the 15-mer library resulted in the enrichment of LeY-binding phages as well (data not shown).

3.2. ELISA measurements

Clones binding to β -estradiol, testosterone, LeY, LT- β , ESL-1 and BSA were further analyzed and characterized as described in Example 2 for FITC. ELISA data for anti- β -estradiol and anti-ESL-1 antibodies are shown in Fig. 18. In one experiment, selectivity and cross-reactivity of binding scFv fragments were tested. For this purpose, an ELISA plate was coated with FITC, testosterone, β -estradiol, BSA, and ESL-1, with 5 wells for each antigen arranged in 5 rows, and 5 antibodies, one against each of the antigens, were screened against each of the antigens. Fig. 19

shows the specific binding of the antibodies to the antigen it was selected for, and the low cross-reactivity with the other four antigens.

3.3 Sequence analysis

The sequencing data of several clones against β -estradiol (34 clones), testosterone (12 clones), LT- β (23 clones), ESL-1 (34 clones), and BSA (10 clones) are given in Figures 20 to 24.

Example 4: Vector Construction

To be able to take advantage of the modularity of the consensus gene repertoire, a vector system had to be constructed which could be used in phage display screening of HuCAL libraries and subsequent optimization procedures. Therefore, all necessary vector elements such as origins of single-stranded or double-stranded replication, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, or detection tags had to be made compatible with the restriction site pattern of the modular consensus genes. Figure 25 shows a schematic representation of the pCAL vector system and the arrangement of vector modules and restriction sites therein. Figure 25a shows a list of all restriction sites which are already incorporated into the consensus genes or the vector elements as part of the modular system or which are not yet present in the whole system. The latter could be used in a later stage for the introduction of or within new modules.

4.1 Vector modules

A series of vector modules was constructed where the restriction sites flanking the gene sub-elements of the HuCAL genes were removed, the vector modules themselves being flanked by unique restriction sites. These modules were constructed either by gene synthesis or by mutagenesis of templates. Mutagenesis was done by add-on PCR, by site-directed mutagenesis (Kunkel et al., 1991) or multisite oligonucleotide-mediated mutagenesis (Sutherland et al., 1995; Perlak, 1990) using a PCR-based assembly method.

Figure 26 contains a list of the modules constructed. Instead of the terminator module M9 (HindIII-*lpp*-PacI), a larger cassette M9II was prepared to introduce FseI as additional restriction site. M9II can be cloned via HindIII/BsrGI.

All vector modules were characterized by restriction analysis and sequencing. In the case of module M11-II, sequencing of the module revealed a two-base difference in positions 164/65 compared to the sequence database of the template. These two different bases (CA → GC) created an additional BanII site. Since the same two-base difference occurs in the *f1* origin of other bacteriophages, it can be assumed that the two-base difference was present in the template and not created by mutagenesis during cloning. This BanII site was removed by site-directed mutagenesis, leading to module M11-III. The BssSI site of module M14 could initially not be removed without impact on the function of the ColE1 origin, therefore M14-Ext2 was used for cloning of the first pCAL vector series. Figures 29 to 34 are showing the functional maps and sequences of the modules used for assembly of the modular vector pCAL4 (see below). The functional maps and sequences of additional modules can be found in Figure 35a. Figure 35b contains a list of oligonucleotides and primers used for the synthesis of the modules.

4.2 Cloning vector pMCS

To be able to assemble the individual vector modules, a cloning vector pMCS containing a specific multi-cloning site (MCS) was constructed. First, an MCS cassette (Fig. 27) was made by gene synthesis. This cassette contains all those restriction sites in the order necessary for the sequential introduction of all vector modules and can be cloned via the 5'-HindIII site and a four base overhang at the 3'-end compatible with an AatII site. The vector pMCS (Figure 28) was constructed by digesting pUC19 with AatII and HindIII, isolating the 2174 base pair fragment containing the *bla* gene and the ColE1 origin, and ligating the MCS cassette.

4.3 Cloning of modular vector pCAL4

This was cloned step by step by restriction digest of pMCS and subsequent ligation of the modules M1 (via AatII/XbaI), M7III (via EcoRI/HindIII), and M9II (via HindIII/BsrGI), and M11-II (via BsrGI/NheI). Finally, the *bla* gene was replaced by the *cat* gene module M17 (via AatII/BglII), and the wild type ColE1 origin by module M14-Ext2 (via BglII/NheI). Figure 35 is showing the functional map and the sequence of pCAL4.

4.4 Cloning of low-copy number plasmid vectors pCALO

A series of low-copy number plasmid vectors was constructed in a similar way using the p15A module M12 instead of the ColE1 module M14-Ext2. Figure 35a is showing the functional maps and sequences of the vectors pCALO1 to pCALO3.

Example 5: Construction of a HuCAL scFv Library

5.1. Cloning of all 49 HuCAL scFv fragments

All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes were assembled as described for the HuCAL VH3-V κ 2 scFv in Example 2 and inserted into the vector pBS12, a modified version of the pLisc series of antibody expression vectors (Skerra et al., 1991).

5.2 Construction of a CDR cloning cassette

For replacement of CDRs, a universal β -lactamase cloning cassette was constructed having a multi-cloning site at the 5'-end as well as at the 3'-end. The 5'-multi-cloning site comprises all restriction sites adjacent to the 5'-end of the HuCAL VH and VL CDRs, the 3'-multi-cloning site comprises all restriction sites adjacent to the 3' end of the HuCAL VH and VL CDRs. Both 5'- and 3'-multi-cloning site were prepared as cassettes via add-on PCR using synthetic oligonucleotides as 5'- and 3'-primers using wild type β -lactamase gene as template. Figure 36 shows the functional map and the sequence of the cassette bla-MCS.

5.3. Preparation of VL-CDR3 library cassettes

The VL-CDR3 libraries comprising 7 random positions were generated from the PCR fragments using oligonucleotide templates V κ 1&V κ 3, V κ 2 and V κ 4 and primers O_K3L_5 and O_K3L_3 (Fig. 37) for the V κ genes, and V λ and primers O_L3L_5 (5'-GCAGAAGGCGAACGTCC-3') and O_L3LA_3 (Fig. 38) for the V λ genes. Construction of the cassettes was performed as described in Example 2.3.

5.4 Cloning of HuCAL scFv genes with VL-CDR3 libraries

Each of the 49 single-chains was subcloned into pCAL4 via XbaI/EcoRI and the VL-CDR3 replaced by the β -lactamase cloning cassette via BbsI/MscI, which was then replaced by the corresponding VL-CDR3 library cassette synthesized as described above. This CDR replacement is described in detail in Example 2.3 where the cal gene was used.

5.5 Preparation of VH-CDR3 library cassette

The VH-CDR3 libraries were designed and synthesized as described in Example 2.3.

5.6 Cloning of HuCAL scFv genes with VL- and VH-CDR3 libraries

Each of the 49 single-chain VL-CDR3 libraries was digested with BssHII/StyI to replace VH-CDR3. The "dummy" cassette digested with BssHII/StyI was inserted, and was then replaced by a corresponding VH-CDR3 library cassette synthesized as described above.

Example 6: Expression tests

Expression and toxicity studies were performed using the scFv format VH-linker-VL. All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes assembled as described in Example 5 were inserted into the vector pBS13, a modified version of the pLisc series of antibody expression vectors (Skerra et al., 1991). A map of this vector is shown in Fig. 39.

E. coli JM83 was transformed 49 times with each of the vectors and stored as glycerol stock. Between 4 and 6 clones were tested simultaneously, always including the clone H3k2, which was used as internal control throughout. As additional control, the McPC603 scFv fragment (Knappik & Plückthun, 1995) in pBS13 was expressed under identical conditions. Two days before the expression test was performed, the clones were cultivated on LB plates containing 30 μ g/ml chloramphenicol and 60 mM glucose. Using this plates an 3 ml culture (LB medium

containing 90 μ g chloramphenicol and 60 mM glucose) was inoculated overnight at 37 °C. Next day the overnight culture was used to inoculate 30 ml LB medium containing chloramphenicol (30 μ g/ml). The starting OD_{600nm} was adjusted to 0.2 and a growth temperature of 30 °C was used. The physiology of the cells was monitored by measuring every 30 minutes for 8 to 9 hours the optical density at 600 nm. After the culture reached an OD_{600nm} of 0.5, antibody expression was induced by adding IPTG to a final concentration of 1 mM. A 5 ml aliquot of the culture was removed after 2 h of induction in order to analyze the antibody expression. The cells were lysed and the soluble and insoluble fractions of the crude extract were separated as described in Knappik & Plückthun, 1995. The fractions were assayed by reducing SDS-PAGE with the samples normalized to identical optical densities. After blotting and immunostaining using the α -FLAG antibody M1 as the first antibody (see Ge et al., 1994) and an Fc-specific anti-mouse antiserum conjugated to alkaline phosphatase as the second antibody, the lanes were scanned and the intensities of the bands of the expected size (appr. 30 kDa) were quantified densitometrically and tabulated relative to the control antibody (see Fig. 40).

Example 7: Optimization of Fluorescein Binders

7.1. Construction of L-CDR3 and H-CDR2 library cassettes

A L-CDR3 library cassette was prepared from the oligonucleotide template CDR3L (5'-TGGAAGCTGAAGACGTGGGCGTATTATTGCCAGCAG(TR5)(TRI)₄CCG(TRI)-TTTGGCCAGGGTACGAAAGTT-3') and primer 5'-AACTTTCGTACCCTGGCC-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (TR5) comprised a trinucleotide mixture representing the 5 codons for Ala, Arg, His, Ser, and Tyr.

A H-CDR2 library cassette was prepared from the oligonucleotide template CDRsH (5'-AGGGTCTCGAGTGGGTGAGC(TRI)ATT(TRI)_{2,3}(6)₂(TRI)ACC(TRI)TATGCGGATAGCGTGAAAGGCCGTTTTACCATTTACGTGATAATTTCGAAAAACACCA-3'), and primer 5'-TGGTGTTTTTCGAATTATCA-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (6) comprised the incorporation of (A/G) (A/C/G) T, resulting in the formation of 6 codons for Ala, Asn, Asp, Gly, Ser, and Thr, and the length distribution being obtained by performing one substoichiometric coupling of the (TRI) mixture during synthesis, omitting the capping step normally used in DNA synthesis.

DNA synthesis was performed on a 40 nmole scale, oligos were dissolved in TE buffer, purified via gel filtration using spin columns (S-200), and the DNA concentration determined by OD measurement at 260 nm (OD 1.0 = 40 μ g/ml).

10 nmole of the oligonucleotide templates and 12 nmole of the corresponding primers were mixed and annealed at 80°C for 1 min, and slowly cooled down to 37°C within 20 to 30 min. The fill-in reaction was performed for 2 h at 37°C using Klenow polymerase (2.0 μ l) and 250 nmole of each dNTP. The excess of dNTPs was removed by gel filtration using Nick-Spin columns (Pharmacia), and the double-stranded DNA digested with BbsI/MscI (L-CDR3), or XhoI/SfuI (H-CDR2) over night at 37°C. The cassettes were purified via Nick-Spin columns (Pharmacia), the concentration determined by OD measurement, and the cassettes aliquoted (15 pmole) for being stored at -80°C.

7.2 Library cloning:

DNA was prepared from the collection of FITC binding clones obtained in Example 2 (approx. 10^4 to clones). The collection of scFv fragments was isolated via XbaI/EcoRI digest. The vector pCAL4 (100 fmole, 10 μ g) described in Example 4.3 was similarly digested with XbaI/EcoRI, gel-purified and ligated with 300 fmole of the scFv fragment collection over night at 16°C. The ligation mixture was isopropanol precipitated, air-dried, and the pellets were redissolved in 100 μ l of dd H₂O. The ligation mixture was mixed with 1 ml of freshly prepared electrocompetent SCS 101 cells (for optimization of L-CDR3), or XL1 Blue cells (for optimization of H-CDR2) on ice. One round of electroporation was performed and the transformants were eluted in SOC medium, shaken at 37°C for 30 minutes, and an aliquot plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9 hrs. The number of transformants was 5×10^4 .

Vector DNA (100 μ g) was isolated and digested (sequence and restriction map of scH3 κ 2 see Figure 8) with BbsI/MscI for optimization of L-CDR3, or XhoI/NspV for optimization of H-CDR2. 10 μ g of purified vector fragments (5 pmole) were ligated with 15 pmole of the L-CDR3 or H-CDR2 library cassettes over night at 16°C. The ligation mixtures were isopropanol precipitated, air-dried, and the pellets were redissolved in 100 μ l of dd H₂O. The ligation mixtures were mixed with 1 ml of freshly prepared electrocompetent XL1 Blue cells on ice. Electroporation was performed and the transformants were eluted in SOC medium and shaken at 37°C for 30 minutes. An aliquot was plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9

hrs. The number of transformants (library size) was greater than 10^8 for both libraries. The libraries were stored as glycerol cultures.

7.3. Biopanning

This was performed as described for the initial H3 κ 2 H-CDR3 library in Example 2.1. Optimized scFvs binding to FITC could be characterized and analyzed as described in Example 2.2 and 2.3, and further rounds of optimization could be made if necessary.

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Table 1A: Human kappa germline gene segments

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
Vk1-1	9	1	O8; O18; DPK1
Vk1-2	1	1	L14; DPK2
Vk1-3	2	1	L15(1); HK101; HK146; HK189
Vk1-4	9	1	L11
Vk1-5	2	1	A30
Vk1-6	1	1	LFVK5
Vk1-7	1	1	LFVK431
Vk1-8	1	1	L1; HK137
Vk1-9	1	1	A20; DPK4
Vk1-10	1	1	L18; Va"
Vk1-11	1	1	L4; L18; Va'; V4a
Vk1-12	2	1	L5; L19(1); Vb; Vb4; DPK5; L19(2); Vb"; DPK6
Vk1-13	2	1	L15(2); HK134; HK166; DPK7
Vk1-14	8	1	L8; Vd; DPK8
Vk1-15	8	1	L9; Ve
Vk1-16	1	1	L12(1); HK102; V1
Vk1-17	2	1	L12(2)
Vk1-18	1	1	O12a (V3b)
Vk1-19	6	1	O2; O12; DPK9
Vk1-20	2	1	L24; Ve"; V13; DPK10
Vk1-21	1	1	O4; O14
Vk1-22	2	1	L22
Vk1-23	2	1	L23
Vk2-1	1	2	A2; DPK12
Vk2-2	6	2	O1; O11(1); DPK13
Vk2-3	6	2	O12(2); V3a
Vk2-4	2	2	L13
Vk2-5	1	2	DPK14
Vk2-6	4	2	A3; A19; DPK15
Vk2-7	4	2	A29; DPK27
Vk2-8	4	2	A13
Vk2-9	1	2	A23

Table 1A: (continued)

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
Vk2-10	4	2	A7; DPK17
Vk2-11	4	2	A17; DPK18
Vk2-12	4	2	A1; DPK19
Vk3-1	11	3	A11; humkv305; DPK20
Vk3-2	1	3	L20; Vg"
Vk3-3	2	3	L2; L16; humkv328; humkv328h2; humkv328h5; DPK21
Vk3-4	11	3	A27; humkv325; VkrF; DPK22
Vk3-5	2	3	L25; DPK23
Vk3-6	2	3	L10(1)
Vk3-7	7	3	L10(2)
Vk3-8	7	3	L6; Vg
Vk4-1	3	4	B3; VklV; DPK24
Vk5-1	10	5	B2; EV15
Vk6-1	12	6	A14; DPK25
Vk6-2	12	6	A10; A26; DPK26
Vk7-1	5	7	B1

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Table 1B: Human lambda germline gene segments

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
DPL1	1	1	
DPL2	1	1	HUMLV1L1
DPL3	1	1	HUMLV122
DPL4	1	1	VLAMBDA 1.1
HUMLV117	2	1	
DPL5	1	1	HUMLV117D
DPL6	1	1	
DPL7	1	1	IGLV1S2
DPL8	1	1	HUMLV1042
DPL9	1	1	HUMLV101
DPL10	1	2	
VLAMBDA 2.1	3	2	
DPL11	1	2	
DPL12	1	2	
DPL13	1	2	
DPL14	1	2	
DPL16	1	3	Humlv418; IGLV3S1
DPL23	1	3	VI III.1
Humlv318	4	3	
DPL18	1	7	4A; HUMIGLVA
DPL19	1	7	
DPL21	1	8	VL8.1
HUMLV801	5	8	
DPL22	1	9	
DPL24	1	unassigned	VLAMBDA N.2
gVLX-4.4	6	10	

Table 1C: Human heavy chain germline gene segments

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
VH1-12-1	19	1	DP10; DA-2; DA-6
VH1-12-8	22	1	RR.VH1:2
VH1-12-2	6	1	hv1263
VH1-12-9	7	1	YAC-7; RR.VH1.1; 1-69
VH1-12-3	19	1	DP3
VH1-12-4	19	1	DP21; 4d275a; VH7a
VH1-12-5	18	1	I-4.1b; V1-4.1b
VH1-12-6	21	1	1D37; VH7b ; 7-81; YAC-10
VH1-12-7	19	1	DP14; VH1GRR; V1-18
VH1-13-1	10	1	71-5; DP2
VH1-13-2	10	1	E3-10
VH1-13-3	19	1	DP1
VH1-13-4	12	1	V35
VH1-13-5	8	1	V1-2b
VH1-13-6	18	1	I-2; DP75
VH1-13-7	21	1	V1-2
VH1-13-8	19	1	DP8
VH1-13-9	3	1	1-1
VH1-13-10	19	1	DP12
VH1-13-11	15	1	V13C
VH1-13-12	18	1	I-3b; DP25; V1-3b
VH1-13-13	3	1	1-92
VH1-13-14	18	1	I-3; V1-3
VH1-13-15	19	1	DP15; V1-8
VH1-13-16	3	1	21-2; 3-1; DP7; V1-46
VH1-13-17	16	1	HC3
VH1-13-18	19	1	DP4; 7-2; V1-45
VH1-13-19	27	1	COS 5
VH1-1X-1	19	1	DP5; 1-24P
VH2-21-1	18	2	II-5b
VH2-31-1	2	2	VH2S12-1
VH2-31-2	2	2	VH2S12-7
VH2-31-3	2	2	VH2S12-9; DP27
VH2-31-4	2	2	VH2S12-10
VH2-31-5	14	2	VH2-26; DP26; 2-26
VH2-31-6	15	2	VH2-26

Table 1C: (continued)

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
VH2-31-7	19	2	DP28; DA-7
VH2-31-14	7	2	YAC-3; 2-70
VH2-31-8	2	2	VH2S12-5
VH2-31-9	2	2	VH2S12-12
VH2-31-10	18	2	II-5; V2-5
VH2-31-11	2	2	VH2S12-2; VH2S12-8
VH2-31-12	2	2	VH2S12-4; VH2S12-6
VH2-31-13	2	2	VH2S12-14
VH3-11-1	13	3	v65-2; DP44
VH3-11-2	19	3	DP45
VH3-11-3	3	3	13-2; DP48
VH3-11-4	19	3	DP52
VH3-11-5	14	3	v3-13
VH3-11-6	19	3	DP42
VH3-11-7	3	3	8-18; YAC-5; 3-66
VH3-11-8	14	3	V3-53
VH3-13-1	3	3	22-28; DP35; V3-11
VH3-13-5	19	3	DF59; VH19; V3-35
VH3-13-6	25	3	f1-p1; DP61
VH3-13-7	19	3	DP46; GL-SJ2; COS 8; hv3005; hv3005f3; 3d21b; 56p1
VH3-13-8	24	3	VH26
VH3-13-9	5	3	vh26c
VH3-13-10	19	3	DP47; VH26; 3-23
VH3-13-11	3	3	1-91
VH3-13-12	19	3	DP58
VH3-13-13	3	3	1-91H; DP49; 3-30; 3d28.1
VH3-13-14	24	3	301939; DP50; 3-33; 3d277
VH3-13-15	27	3	C15.3
VH3-13-16	19	3	DP51
VH3-13-17	16	3	F11
VH3-13-18	19	3	DP33; COS 6; 3-74; DA-8
VH3-13-19	19	3	DP34; VH3-11; V3-7
VH3-13-20	14	3	V3-64; YAC-6
VH3-13-21	14	3	V3-43
VH3-13-22	14	3	V3-43; DP33
VH3-13-23	14	3	V3-33

Table 1C: (continued)

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
VH3-13-24	14	3	V3-21; DP77
VH3-13-25	14	3	V3-20; DP32
VH3-13-26	14	3	V3-9; DP31
VH3-14-1	3	3	12-2; DP29; 3-72; DA-3
VH3-14-4	7	3	YAC-9; 3-73; MTGL
VH3-14-2	4	3	VHD26
VH3-14-3	19	3	DP20
VH3-1X-1	1	3	LSG8.1; LSG9.1; LSG10.1; HUM12IGVH; HUM13IGVH
VH3-1X-2	1	3	LSG11.1; HUM4IGVH
VH3-1X-3	3	3	9-1; DP38; LSG7.1; RCG1.1; LSG1.1; LSG3.1; LSG5.1; HUM115IGVH; HUM2IGVH; HUM9IGVH
VH3-1X-4	1	3	LSG4.1
VH3-1X-5	1	3	LSG2.1
VH3-1X-6	1	3	LSG6.1; HUM10IGVH
VH3-1X-7	18	3	3-15; V3-15
VH3-1X-8	1	3	LSG12.1; HUM5IGVH
VH3-1X-9	14	3	V3-49
VH4-11-1	22	4	Tou-VH4.21
VH4-11-2	17	4	VH4.21; DP63; VH5; 4d76; V4-34
VH4-11-3	23	4	4.44
VH4-11-4	23	4	4.44.3
VH4-11-5	23	4	4.33
VH4-11-6	23	4	4.37
VH4-11-7	18	4	IV-4; 4.35; V4-4
VH4-11-8	17	4	VH4.11; 3d197d; DP71; 58p2
VH4-11-9	20	4	H7
VH4-11-10	20	4	H7
VH4-11-11	20	4	H7
VH4-11-12	17	4	V4.16
VH4-11-13	23	4	4.4
VH4-11-14	17	4	V4.15
VH4-11-15	11	4	5.
VH4-11-16	10	4	7.1.1; V4-59
VH4-21-1	11	4	11
VH4-21-2	17	4	VH4.17; VH4.23; 4d255; 4.40; DP69
VH4-21-3	17	4	VH4.19; 79; V4-4b

Table 1C: (continued)

Used Name ¹	Reference ²	Family ³	Germline genes ⁴
VH4-21-4	19	4	DP70; 4d68; 4.41
VH4-21-5	19	4	DP67; VH4-4B
VH4-21-6	17	4	VH4.22; VHSP; VH-JA
VH4-21-7	17	4	VH4.13; 1-9II; 12G-1; 3d28d; 4.42; DP68; 4-28
VH4-21-8	26	4	hv4005; 3d24d
VH4-21-9	17	4	VH4.14
VH4-31-1	23	4	4.34; 3d230d; DP78
VH4-31-2	23	4	4.34.2
VH4-31-3	19	4	DP64; 3d216d
VH4-31-4	19	4	DP65; 4-31; 3d277d
VH4-31-5	23	4	4.33; 3d75d
VH4-31-6	20	4	H10
VH4-31-7	20	4	H11
VH4-31-8	23	4	4.31
VH4-31-9	23	4	4.32
VH4-31-10	20	4	3d277d
VH4-31-11	20	4	3d216d
VH4-31-12	20	4	3d279d
VH4-31-13	17	4	VH4.18; 4d154; DP79
VH4-31-14	8	4	V4-29
VH4-31-15	11	4	2-1; DP79
VH4-31-16	23	4	4.35
VH4-31-17	17	4	V4.12
VH4-31-18	10	4	71-2; DP66
VH4-31-19	23	4	4.36
VH4-31-20	8	4	V4-21
VH5-12-1	9	5	VH551; DP73; VHVCW; 51-R1; VHVLB; VHVCH; VHVTT; VH5AU; VHVBLK; VhAU; V5-51
VH5-12-2	17	5	VH558
VH5-12-3	3	5	1-1; DP80; 5-78
VH5-12-4	9	5	VH5-2; VHVRG; VHVMW; 5-2R1
VH6-35-1	4	6	VH6-3; VH6; VHVIIS; VHVITE; VHVUIB; VHVICH; VHVICW; VH6FLK; VHVIMW; DP74; 6-1G1; V6-1

Table 2A: rearranged human kappa sequences

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
III-3R	108	1	O8	1	1,1%	70
No.86	109	1	O8	3	3,2%	80
AU	108	1	O8	6	6,3%	103
ROY	108	1	O8	6	6,3%	43
IC4	108	1	O8	6	6,3%	70
HIV-B26	106	1	O8	3	3,2%	8
GRI	108	1	O8	8	8,4%	30
AG	106	1	O8	8	8,6%	116
REI	108	1	O8	9	9,5%	86
CLL PATIENT 16	88	1	O8	2	2,3%	122
CLL PATIENT 14	87	1	O8	2	2,3%	122
CLL PATIENT 15	88	1	O8	2	2,3%	122
GM4672	108	1	O8	11	11,6%	24
HUM. YFC51.1	108	1	O8	12	12,6%	110
LAY	108	1	O8	12	12,6%	48
HIV-b13	106	1	O8	9	9,7%	8
MAL-NaCl	108	1	O8	13	13,7%	102
STRab SA-1A	108	1	O2	0	0,0%	120
HuVHCAMP	108	1	O8	13	13,7%	100
CRO	108	1	O2	10	10,5%	30
Am107	108	1	O2	12	12,6%	108
WALKER	107	1	O2	4	4,2%	57
III-2R	109	1	A20	0	0,0%	70
FOG1-A4	107	1	A20	4	4,2%	41
HK137	95	1	L1	0	0,0%	10
CEA4-8A	107	1	O2	7	7,4%	41
Va'	95	1	L4	0	0,0%	90
TR1.21	108	1	O2	4	4,2%	92
HAU	108	1	O2	6	6,3%	123
HK102	95	1	L12(1)	0	0,0%	9
H20C3K	108	1	L12(2)	3	3,2%	125
CHEB	108	1	O2	7	7,4%	5
HK134	95	1	L15(2)	0	0,0%	10
TEL9	108	1	O2	9	9,5%	73

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
TR1.32	103	1	O2	3	3,2%	92
RF-KES1	97	1	A20	4	4,2%	121
WES	108	1	L5	10	10,5%	61
DILp1	95	1	O4	1	1,1%	70
SA-4B	107	1	L12(2)	8	8,4%	120
HK101	95	1	L15(1)	0	0,0%	9
TR1.23	108	1	O2	5	5,3%	92
HF2-1/17	108	1	A30	0	0,0%	4
2E7	108	1	A30	1	1,1%	62
33.C9	107	1	L12(2)	7	7,4%	126
3D6	105	1	L12(2)	2	2,1%	34
I-2a	108	1	L8	8	8,4%	70
RF-KL1	97	1	L8	4	4,2%	121
TNF-E7	108	1	A30	9	9,5%	41
TR1.22	108	1	O2	7	7,4%	92
HIV-B35	105	1	O2	2	2,2%	8
HIV-b22	106	1	O2	2	2,2%	8
HIV-b27	106	1	O2	2	2,2%	8
HIV-B8	107	1	O2	10	10,8%	8
HIV-b8	107	1	O2	10	10,8%	8
RF-SJ5	95	1	A20	5	5,3%	113
GAL(I)	108	1	A30	6	6,3%	64
R3.5H5G	103	1	O2	6	6,3%	70
HIV-b14	106	1	A20	2	2,2%	8
TNF-E1	105	1	L5	8	8,4%	41
WEA	108	1	A30	8	8,4%	37
EU	103	1	L12(2)	5	5,3%	40
FOG1-G8	103	1	L8	11	11,6%	41
1X7RG1	103	1	L1	8	8,4%	70
BLI	103	1	L8	3	3,2%	72
KUE	103	1	L12(2)	11	11,6%	32
LUNm01	103	1	L12(2)	10	10,5%	6
HIV-b1	105	1	A20	4	4,3%	8
HIV-s4	103	1	O2	2	2,2%	8

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
CAR	107	1	L12(2)	11	11,7%	79
BR	107	1	L12(2)	11	11,6%	50
CLL PATIENT 10	88	1	O2	0	0,0%	122
CLL PATIENT 12	88	1	O2	0	0,0%	122
KING	108	1	L12(2)	12	12,6%	30
V13	95	1	L24	0	0,0%	46
CLL PATIENT 11	87	1	O2	0	0,0%	122
CLL PATIENT 13	87	1	O2	0	0,0%	122
CLL PATIENT 9	89	1	O12	1	1,1%	122
HIV-B2	106	1	A20	9	9,7%	8
HIV-b2	106	1	A20	9	9,7%	8
CLL PATIENT 5	88	1	A20	1	1,1%	122
CLL PATIENT 1	88	1	L8	2	2,3%	122
CLL PATIENT 2	88	1	L8	0	0,0%	122
CLL PATIENT 7	88	1	L5	0	0,0%	122
CLL PATIENT 8	88	1	L5	0	0,0%	122
HIV-b5	105	1	L5	11	12,0%	8
CLL PATIENT 3	87	1	L8	1	1,1%	122
CLL PATIENT 4	88	1	L9	0	0,0%	122
CLL PATIENT 18	85	1	L9	6	7,1%	122
CLL PATIENT 17	85	1	L12(2)	7	8,1%	122
HIV-b20	107	3	A27	11	11,7%	8
2C12	103	1	L12(2)	20	21,1%	68
1B11	103	1	L12(2)	20	21,1%	68
1H1	103	1	L12(2)	21	22,1%	68
2A12	103	1	L12(2)	21	22,1%	68
CUR	100	3	A27	0	0,0%	66
GLO	100	3	A27	0	0,0%	16
RF-TS1	90	3	A27	0	0,0%	121
GAR	100	3	A27	0	0,0%	67
FLO	100	3	A27	0	0,0%	66
PIE	100	3	A27	0	0,0%	91
HAH 14.1	100	3	A27	1	1,0%	51
HAH 14.2	100	3	A27	1	1,0%	51

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
HAH 16.1	105	3	A27	1	1,0%	51
NOV	109	3	A27	1	1,0%	52
33.F12	108	3	A27	1	1,0%	126
8E10	110	3	A27	1	1,0%	25
TH3	109	3	A27	1	1,0%	25
HIC (R)	103	3	A27	0	0,0%	51
SON	110	3	A27	1	1,0%	67
PAY	109	3	A27	1	1,0%	66
GOT	109	3	A27	1	1,0%	67
mAbA6H4C5	109	3	A27	1	1,0%	12
BOR'	109	3	A27	2	2,1%	84
RF-SJ3	95	3	A27	2	2,1%	121
SIE	109	3	A27	2	2,1%	15
ESC	109	3	A27	2	2,1%	98
HEW'	113	3	A27	2	2,1%	98
YES8c	103	3	A27	3	3,1%	33
TI	109	3	A27	3	3,1%	114
mAb113	109	3	A27	3	3,1%	71
HEW	109	3	A27	0	0,0%	94
BRO	109	3	A27	0	0,0%	94
ROB	109	3	A27	0	0,0%	94
NG9	91	3	A27	4	4,2%	11
NEU	109	3	A27	4	4,2%	66
WOL	109	3	A27	4	4,2%	2
35G6	109	3	A27	4	4,2%	59
RF-SJ4	109	3	A27	0	0,0%	88
KAS	109	3	A27	4	4,2%	84
BRA	109	3	A27	1	1,1%	94
HAH	109	3	A27	1	1,1%	94
HIC	109	3	A27	0	0,0%	94
FS-2	109	3	A27	6	6,3%	87
JH'	109	3	A27	6	6,3%	38
EV1-15	109	3	A27	6	6,3%	83
SCA	109	3	A27	6	6,3%	65

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
mAb112	109	3	A27	6	6,3%	71
SIC	103	3	A27	3	3,3%	94
SA-4A	109	3	A27	6	6,3%	120
SER	108	3	A27	6	6,3%	98
GOL'	109	3	A27	7	7,3%	82
B5G10K	105	3	A27	9	9,7%	125
HG2B10K	110	3	A27	-9	9,4%	125
Taykv322	105	3	A27	5	5,4%	52
CLL PATIENT 24	89	3	A27	1	1,1%	122
HIV-b24	107	3	A27	7	7,4%	8
HIV-b6	107	3	A27	7	7,4%	8
Taykv310	99	3	A27	1	1,1%	52
KA3D1	108	3	L6	0	0,0%	85
19.E7	107	3	L6	0	0,0%	126
rsv6L	109	3	A27	12	12,5%	7
Taykv320	98	3	A27	1	1,2%	52
Vh	98	3	L10(2)	0	0,0%	89
LS8	103	3	L6	1	1,1%	109
LS1	103	3	L6	1	1,1%	109
LS2S3-3	103	3	L6	2	2,1%	99
LS2	103	3	L6	1	1,1%	109
LS7	103	3	L6	1	1,1%	109
LS2S3-4d	103	3	L6	2	2,1%	99
LS2S3-4a	103	3	L6	2	2,1%	99
LS4	103	3	L6	1	1,1%	109
LS6	103	3	L6	1	1,1%	109
LS2S3-10a	103	3	L6	2	2,1%	99
LS2S3-8c	103	3	L6	2	2,1%	99
LS5	103	3	L6	1	1,1%	109
LS2S3-5	103	3	L6	3	3,2%	99
LUNm03	103	3	A27	13	13,5%	6
IARC/BL41	103	3	A27	13	13,7%	55
slkv22	9	3	A27	3	3,5%	13
POP	103	3	L6	4	4,2%	111

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
LS2S3-10b	107	3	L6	3	3,2%	99
LS2S3-8f	107	3	L6	3	3,2%	99
LS2S3-12	107	3	L6	3	3,2%	99
HIV-B30	107	3	A27	11	11,7%	8
HIV-B20	107	3	A27	11	11,7%	8
HIV-b3	103	3	A27	11	11,7%	8
HIV-s6	104	3	A27	9	9,9%	8
YSE	107	3	L2/L16	1	1,1%	72
POM	109	3	L2/L16	9	9,4%	53
Humkv328	95	3	L2/L16	1	1,1%	19
CLL	109	3	L2/L16	3	3,2%	47
LES	90	3	L2/L16	3	3,2%	38
HIV-s5	104	3	A27	11	12,1%	8
HIV-s7	109	3	A27	11	12,1%	8
slkv1	99	3	A27	7	8,1%	13
Humka31es	95	3	L2/L16	4	4,2%	18
slkv12	101	3	A27	8	9,2%	13
RF-TS2	95	3	L2/L16	3	3,2%	121
II-1	109	3	L2/L16	4	4,2%	70
HIV-s3	101	3	A27	13	14,3%	8
RF-TMC1	9	3	L5	10	10,5%	121
GER	109	3	L2/L16	7	7,4%	75
GF4/1.1	109	3	L2/L16	8	8,4%	36
mAb114	109	3	L2/L16	6	6,3%	71
HIV-loop13	109	3	L2/L16	7	7,4%	8
bkv16	8	3	L5	1	1,2%	13
CLL PATIENT 29	8	3	L5	1	1,2%	122
slkv9	9	3	L5	3	3,5%	13
bkv17	9	3	L5	1	1,2%	13
slkv14	9	3	L5	1	1,2%	13
slkv16	101	3	L5	2	2,3%	13
bkv33	101	3	L5	4	4,7%	13
slkv15	9	3	L5	2	2,3%	13
bkv6	101	3	L5	3	3,5%	13

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
R6B8K	108	3	L2/L16	12	12,6%	125
AL 700	107	3	L2/L16	9	9,5%	117
slkv11	100	3	L2/L16	3	3,5%	13
slkv4	97	3	L6	4	4,8%	13
CLL PATIENT 26	87	3	L2/L16	1	1,1%	122
AL Se124	103	3	L2/L16	9	9,5%	117
slkv13	100	3	L2/L16	6	7,0%	13
bkv7	100	3	L2/L16	5	5,8%	13
bkv22	100	3	L2/L16	6	7,0%	13
CLL PATIENT 27	84	3	L2/L16	0	0,0%	122
bkv35	100	3	L6	8	9,3%	13
CLL PATIENT 25	87	3	L2/L16	4	4,6%	122
slkv3	86	3	L2/L16	7	8,1%	13
slkv7	99	1	C2	7	8,1%	13
HuFd79	111	3	L2/L16	24	24,2%	21
RAD	99	3	A27	9	10,3%	78
CLL PATIENT 28	83	3	L2/L16	4	4,8%	122
REE	104	3	L2/L16	25	27,2%	95
FR4	99	3	A27	8	9,2%	77
MD3.3	92	3	L6	1	1,3%	54
MD3.1	92	3	L6	0	0,0%	54
GA3.6	92	3	L6	2	2,6%	54
M3.5N	92	3	L6	3	3,8%	54
WEI'	81	3	A27	0	0,0%	65
MD3.4	92	3	L2/L16	1	1,3%	54
MD3.2	91	3	L6	3	3,8%	54
VER	92	3	A27	19	22,4%	20
CLL PATIENT 30	73	3	L6	3	3,8%	122
M3.1N	92	3	L2/L16	1	1,3%	54
MD3.6	91	3	L2/L16	0	0,0%	54
MD3.8	91	3	L2/L16	0	0,0%	54
GA3.4	93	3	L6	7	9,0%	54
M3.6N	91	3	A27	0	0,0%	54
MD3.10	91	3	A27	0	0,0%	54

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
MD3.13	91	3	A27	0	0,0%	54
MD3.7	93	3	A27	0	0,0%	54
MD3.9	93	3	A27	0	0,0%	54
GA3.1	93	3	A27	6	7,6%	54
bkv32	101	3	A27	5	5,7%	13
GA3.5	93	3	A27	5	6,3%	54
GA3.7	92	3	A27	7	8,9%	54
MD3.12	92	3	A27	2	2,5%	54
M3.2N	90	3	L6	6	7,8%	54
MD3.5	92	3	A27	1	1,3%	54
M3.4N	91	3	L2/L16	8	10,3%	54
M3.8N	91	3	L2/L16	7	9,0%	54
M3.7N	92	3	A27	3	3,8%	54
GA3.2	92	3	A27	9	11,4%	54
GA3.8	93	3	A27	4	5,1%	54
GA3.3	92	3	A27	8	10,1%	54
M3.3N	92	3	A27	5	6,3%	54
B6	83	3	A27	8	11,3%	78
E29.1 KAPPA	78	3	L2/L16	0	0,0%	22
SCW	108	1	(3)	12	12,6%	31
REI-based CAMPATH-9	107	1	(3)	14	14,7%	39
RZ	107	1	(3)	14	14,7%	50
BI	108	1	(3)	14	14,7%	14
AND	107	1	(2)	13	13,7%	69
2A4	109	1	(2)	12	12,6%	23
KA	109	1	(3)	19	20,0%	107
MEV	109	1	(2)	14	14,7%	29
DEE	106	1	(2)	13	14,0%	76
OU(I0C)	109	1	(2)	18	18,9%	60
HuRSV19VK	111	1	(3)	21	21,0%	115
SP2	10	1	(2)	17	17,9%	93
BJ26	99	1	(3)	21	24,1%	1
NI	112	1	(3)	24	24,2%	106
BMA 0310EUCIV2	100	1	L1/L1)	21	22,3%	105

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
CLL PATIENT 6	71	1	A20	0	0,0%	122
BJ19	85	1	C8	16	21,9%	1
GM 607	113	2	A3	0	0,0%	58
R5A3K	114	2	A3	1	1,0%	125
R1C8K	114	2	A3	1	1,0%	125
VK2.R149	115	2	A3	2	2,0%	118
TR1.6	109	2	A3	4	4,0%	92
TR1.37	101	2	A3	5	5,0%	92
FS-1	115	2	A3	6	6,0%	87
TR1.8	111	2	A3	6	6,0%	92
NIM	112	2	A3	8	8,0%	28
Inc	112	2	A3	11	11,0%	35
TEW	101	2	A3	6	6,4%	96
CUM	111	2	C1	7	6,9%	44
HRF1	71	2	A3	4	5,6%	124
CLL PATIENT 19	81	2	A3	0	0,0%	122
CLL PATIENT 20	81	2	A3	0	0,0%	122
MIL	111	2	A3	16	16,2%	26
FR	111	2	A3	20	20,0%	101
MAL-Urine	81	1	C2	6	8,6%	102
Taykv306	71	3	A7	1	1,6%	52
Taykv312	71	3	A7	1	1,6%	52
HIV-b29	91	3	A7	14	17,5%	8
1-185-37	111	3	A7	0	0,0%	119
1-187-29	111	3	A7	0	0,0%	119
TT117	111	3	A7	9	9,4%	63
HIV-loop8	111	3	A7	16	16,8%	8
rsv23L	111	3	A7	16	16,8%	7
HIV-b7	111	3	A7	14	14,9%	8
HIV-b11	111	3	A7	15	16,0%	8
HIV-LC1	111	3	A7	19	20,2%	8
HIV-LC7	111	3	A7	20	21,3%	8
HIV-LC22	111	3	A7	21	22,3%	8
HIV-LC13	111	3	A7	21	22,3%	8

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
HIV-LC3	107	3	A27	21	22,3%	8
HIV-LC5	107	3	A27	21	22,3%	8
HIV-LC28	107	3	A27	21	22,3%	8
HIV-b4	107	3	A27	22	23,4%	8
CLL PATIENT 31	87	3	A27	15	17,2%	122
HIV-loop2	108	3	L2, L16	17	17,9%	8
HIV-loop35	108	3	L2, L16	17	17,9%	8
HIV-LC11	107	3	A27	23	24,5%	8
HIV-LC24	107	3	A27	23	24,5%	8
HIV-b12	107	3	A27	24	25,5%	8
HIV-LC25	107	3	A27	24	25,5%	8
HIV-b21	107	3	A27	24	25,5%	8
HIV-LC26	107	3	A27	26	27,7%	8
G3D10K	108	1	L1, L2	12	12,6%	125
TT125	108	1	L5	8	8,4%	63
HIV-s2	107	3	A27	28	31,1%	8
265-695	107	1	L5	7	7,4%	3
2-115-19	107	1	A27	2	2,1%	119
rsv13L	107	1	(2)	20	21,1%	7
HIV-b18	108	1	(2)	14	15,1%	8
RF-KL5	98	3	L5	36	36,7%	97
ZM1-1	113	2	A27	7	7,0%	3
HIV-s8	108	1	(3)	16	17,8%	8
K- EV15	95	5	L2	0	0,0%	112
RF-TS3	108	2	A3	0	0,0%	121
HF-21/28	111	2	A27	1	1,0%	17
RPMI6410	112	2	A27	1	1,0%	42
JC11	113	2	A27	1	1,0%	49
O-81	113	2	A27	5	5,0%	45
FK-001	113	4	L3	0	0,0%	81
CD5+.28	108	4	L3	1	1,0%	27
LEN	113	4	L3	1	1,0%	104
UC	113	4	L3	1	1,0%	111
CD5+.5	108	4	L3	1	1,0%	27

Table 2A: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
CD5+.26	101	4	B3	1	1,0%	27
CD5+.12	101	4	B3	2	2,0%	27
CD5+.23	101	4	B3	2	2,0%	27
CD5+.7	101	4	B3	2	2,0%	27
VJI	113	4	B3	3	3,0%	56
LOC	113	4	B3	3	3,0%	72
MAL	113	4	B3	3	3,0%	72
CD5+.6	101	4	B3	3	3,0%	27
H2F	113	4	B3	3	3,0%	70
PB17IV	114	4	B3	4	4,0%	74
CD5+.27	101	4	B3	4	4,0%	27
CD5+.9	101	4	B3	4	4,0%	27
CD5-.28	101	4	B3	5	5,0%	27
CD5-.26	101	4	B3	6	5,9%	27
CD5+.24	101	4	B3	6	5,9%	27
CD5+.10	101	4	B3	6	5,9%	27
CD5-.19	101	4	B3	6	5,9%	27
CD5-.18	101	4	B3	7	6,9%	27
CD5-.16	101	4	B3	8	7,9%	27
CD5-.24	101	4	B3	8	7,9%	27
CD5-.17	101	4	B3	10	9,9%	27
MD4.1	92	4	B3	0	0,0%	54
MD4.4	92	4	B3	0	0,0%	54
MD4.5	92	4	B3	0	0,0%	54
MD4.6	92	4	B3	0	0,0%	54
MD4.7	92	4	B3	0	0,0%	54
MD4.2	92	4	B3	1	1,3%	54
MD4.3	92	4	B3	5	6,3%	54
CLL PATIENT 22	87	2	A17	2	2,3%	122
CLL PATIENT 23	87	2	A17	2	2,4%	122

Table 2B: rearranged human lambda sequences

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
WAH	110	1	DPL3	7	7%	68
1B9/F2	112	1	DPL3	7	7%	9
DIA	112	1	DPL2	7	7%	36
mAb67	89	1	DPL3	0	0%	29
HiH2	110	1	DPL3	12	11%	3
NIG-77	112	1	DPL2	9	9%	72
OKA	112	1	DPL2	7	7%	84
KOL	112	1	DPL2	12	11%	40
T2:C5	111	1	DPL5	0	0%	6
T2:C14	110	1	DPL5	0	0%	6
PR-TS1	110	1	DPL5	0	0%	55
4G12	111	1	DPL5	1	1%	35
KIM46L	112	1	HUMAN117	0	0%	8
Fog-B	111	1	DPL5	3	3%	31
9F2L	111	1	DPL5	3	3%	79
mAb111	110	1	DPL5	3	3%	48
PHOX15	111	1	DPL5	4	4%	49
BL2	111	1	DPL5	4	4%	74
NIG-64	111	1	DPL5	4	4%	72
RF-SJ2	100	1	DPL5	6	6%	78
AL EZI	112	1	DPL5	7	7%	41
ZIM	112	1	HUMAN117	7	7%	18
RF-SJ1	100	1	DPL5	9	9%	78
IGLV1.1	98	1	DPL4	0	0%	1
NEW	112	1	HUMAN117	11	10%	42
CB-201	87	1	DPL2	1	1%	62
MEM	100	1	DPL2	6	6%	50
H210	111	2	DPL10	4	4%	45
NOV	110	2	DPL10	8	8%	25
NEI	111	2	DPL10	8	8%	24
AL MC	110	2	DPL11	6	6%	28
MES	112	2	DPL11	8	8%	84
FOG1-A3	111	2	DPL11	9	9%	27
AL NOV	111	2	DPL11	7	7%	28

Table 2B: (continued)

Name ¹	aa	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
HMST-1	110	2	DPL11	4	4%	82
HBW4-1	100	2	DPL12	9	9%	52
WH	110	2	DPL11	11	11%	34
11-50	110	2	DPL11	7	7%	82
HBp2	110	2	DPL12	8	8%	3
NIG-84	11	2	DPL11	12	11%	73
VIL	112	2	DPL11	9	9%	58
TRO	110	2	DPL12	10	10%	61
ES492	100	2	DPL11	15	15%	76
mAb216	8	2	DPL12	1	1%	7
BSA3	100	3	DPL16	0	0%	49
THY-29	100	3	DPL16	0	0%	27
PR-TS2	103	3	DPL16	0	0%	55
E29.1 LAMBDA	107	3	DPL16	1	1%	13
mAb63	109	3	DPL16	2	2%	29
TEL14	100	3	DPL16	6	6%	49
6H-3C4	104	3	DPL16	7	7%	39
SH	104	3	DPL16	7	7%	70
AL GIL	104	3	DPL16	8	8%	23
H6-3C4	103	3	DPL16	8	8%	83
V-lambda-2.DS	101	2	DPL11	3	3%	15
8.12 ID	100	2	DPL11	3	3%	81
DSC	101	2	DPL11	3	3%	56
PV11	100	2	DPL11	1	1%	56
33.H11	100	2	DPL11	4	4%	81
AS17	100	2	DPL11	7	7%	56
SD6	100	2	DPL11	7	7%	56
KS3	100	2	DPL11	9	9%	56
PV6	100	2	DPL12	5	5%	56
NGD9	100	2	DPL11	7	7%	56
MUC1-1	101	2	DPL11	11	10%	27
A30c	101	2	DPL10	6	6%	56
KS6	100	2	DPL12	6	6%	56
TEL13	100	2	DPL11	11	10%	49

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Table 2B: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
AS7	110	2	DPL12	6	6%	56
MCG	112	2	DPL12	12	11%	20
U266L	110	2	DPL12	13	12%	77
PR-SJ2	110	2	DPL12	14	13%	55
BOH	112	2	DPL12	11	10%	37
TOG	111	2	DPL11	19	18%	53
TEL16	111	2	DPL11	19	18%	49
No.13	110	2	DPL10	14	13%	52
BO	112	2	DPL12	18	17%	80
WIN	112	2	DPL12	17	16%	11
BUR	114	2	DPL12	15	15%	46
NIG-58	110	2	DPL12	20	19%	69
WEIR	112	2	DPL11	26	25%	21
THY-32	111	1	DPL8	8	8%	27
TNF-H9G1	111	1	DPL8	9	9%	27
mAb61	111	1	DPL3	1	1%	29
LV1L1	113	1	DPL2	0	0%	54
HA	113	1	DPL3	14	13%	63
LA1L1	111	1	DPL2	3	3%	54
RHE	112	1	DPL1	17	16%	22
K1B12L	113	1	DPL8	17	16%	79
LOC	113	1	DPL2	15	14%	84
NIG-51	112	1	DPL2	12	11%	67
NEWM	114	1	DPL8	23	22%	10
MD3-4	116	3	DPL23	14	13%	4
COX	112	1	DPL2	13	12%	84
HiH10	116	3	DPL23	13	12%	3
VOR	112	1	DPL2	16	15%	16
AL POL	113	1	DPL2	16	15%	57
CD4-74	111	1	DPL2	19	18%	27
AMYLOID MOL	112	3	DPL23	15	15%	30
OST577	113	3	H318	10	10%	4
NIG-48	113	1	DPL3	42	40%	66
CARR	113	3	DPL23	18	17%	19

6.

Table 2B: (continued)

Name ¹	aa ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
mAb60	106	3	DPL23	14	13%	29
NIG-68	99	3	DPL23	25	26%	32
KERN	107	3	DPL23	26	25%	59
ANT	106	3	DPL23	17	16%	19
LEE	110	3	DPL23	18	17%	85
CLE	94	3	DPL23	17	17%	19
VL8	98	8	DPL21	0	0%	81
MOT	110	3	Hum1318	23	22%	38
GAR	104	3	DPL23	26	25%	33
32.B9	98	8	DPL21	5	5%	81
PUG	108	3	Hum1318	24	23%	19
T1	115	8	HUM1301	52	50%	6
RF-TS7	91	7	DPL23	4	4%	60
YM-1	115	8	HUM1301	51	49%	75
K6H6	112	8	HUM1301	20	19%	44
K5C7	112	8	HUM1301	20	19%	44
K5B8	112	8	HUM1301	20	19%	44
K5G5	112	8	HUM1301	20	19%	44
K4B8	112	8	HUM1301	19	18%	44
K6F5	112	8	HUM1301	17	16%	44
HIL	112	3	DPL23	22	21%	47
KIR	112	3	DPL23	20	19%	19
CAP	112	3	DPL23	19	18%	84
1B8	112	3	DPL23	22	21%	43
SHO	112	3	DPL23	19	18%	19
HAN	112	3	DPL23	20	19%	19
cML23	91	3	DPL23	3	3%	12
PR-SJ1	91	3	DPL23	7	7%	55
BAU	112	3	DPL23	9	9%	5
TEX	91	3	DPL23	8	8%	19
X(PET)	112	3	DPL23	9	9%	51
DOY	112	3	DPL23	9	9%	19
COT	112	3	DPL23	13	12%	19
Pag-1	112	3	Hum1318	5	5%	31

Table 2B: (continued)

Name ¹	a	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
DIS	101	3	Humlv318	2	2%	19
WIT	102	3	Humlv318	7	7%	19
I.RH	102	3	Humlv318	12	11%	19
S1-1	103	3	Humlv318	12	11%	52
DEL	102	3	Humlv318	14	13%	17
TYR	103	3	Humlv318	11	10%	19
J.RH	103	3	Humlv318	13	12%	19
THO	101	2	DPL3	38	36%	26
LBV	101	1	DPL3	38	36%	2
WLT	101	1	DPL3	33	31%	14
SUT	101	2	DPL12	37	35%	65

Table 2C: rearranged human heavy chain sequences

Name ¹	Accession ²	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
21/28	115	1	VH1-13-12	0	0,0%	31
8E10	115	1	VH1-13-12	0	0,0%	31
MUC1-1	117	1	VH1-13-6	4	4,1%	42
gF1	9	1	VH1-13-12	10	10,2%	75
VHGL 1.2	9	1	VH1-13-6	2	2,0%	26
HV1L1	5	1	VH1-13-6	0	0,0%	81
RF-TS7	103	1	VH1-13-6	3	3,1%	96
E55 1.A15	107	1	VH1-12-15	1	1,0%	26
HA1L1	1	1	VH1-13-6	7	7,1%	81
UC	1	1	VH1-13-6	5	5,1%	115
WIL2	1	1	VH1-13-6	6	6,1%	55
R3.5H5G	1	1	VH1-13-6	10	10,2%	70
N89P2	1	1	VH1-13-16	11	11,2%	77
mAb113	1	1	VH1-13-6	10	10,2%	71
LS2S3-3	1	1	VH1-12-7	5	5,1%	98
LS2S3-12a	1	1	VH1-12-7	5	5,1%	98
LS2S3-5	1	1	VH1-12-7	5	5,1%	98
LS2S3-12e	1	1	VH1-12-7	5	5,1%	98
LS2S3-4	1	1	VH1-12-7	5	5,1%	98
LS2S3-10	1	1	VH1-12-7	5	5,1%	98
LS2S3-12d	1	1	VH1-12-7	6	6,1%	98
LS2S3-8	1	1	VH1-12-7	5	5,1%	98
LS2	1	1	VH1-12-7	6	6,1%	113
LS4	1	1	VH1-12-7	6	6,1%	113
LS5	1	1	VH1-12-7	6	6,1%	113
LS1	1	1	VH1-12-7	6	6,1%	113
LS6	1	1	VH1-12-7	6	6,1%	113
LS8	1	1	VH1-12-7	7	7,1%	113
THY-29	1	1	VH1-12-7	0	0,0%	42
1B9/F2	1	1	VH1-12-7	10	10,2%	21
51P1	3	1	VH1-12-1	0	0,0%	105
NEI	1	1	VH1-12-1	0	0,0%	55
AND	1	1	VH1-12-1	0	0,0%	55
L7	1	1	VH1-12-1	0	0,0%	54
L22	1	1	VH1-12-1	0	0,0%	54
L24	1	1	VH1-12-1	0	0,0%	54

Table 2C: (continued)

Name ¹	Computed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
L26	1	VH1-12-1	0	0,0%	54
L33	1	VH1-12-1	0	0,0%	54
L34	1	VH1-12-1	0	0,0%	54
L36	1	VH1-12-1	0	0,0%	54
L39	1	VH1-12-1	0	0,0%	54
L41	1	VH1-12-1	0	0,0%	54
L42	1	VH1-12-1	0	0,0%	54
VHGL 1.8	1	VH1-12-1	0	0,0%	26
783c	1	VH1-12-1	0	0,0%	22
X17115	1	VH1-12-1	0	0,0%	37
L25	1	VH1-12-1	0	0,0%	54
L17	1	VH1-12-1	1	1,0%	54
L30	1	VH1-12-1	1	1,0%	54
L37	1	VH1-12-1	1	1,0%	54
TNF-E7	1	VH1-12-1	2	2,0%	42
mAb111	1	VH1-12-1	7	7,1%	71
III-2R	1	VH1-12-9	3	3,1%	70
KAS	1	VH1-12-1	7	7,1%	79
YES8c	1	VH1-12-1	8	8,2%	34
RF-TS1	1	VH1-12-1	8	8,2%	82
BOR'	1	VH1-12-8	7	7,1%	79
VHGL 1.9	1	VH1-12-1	8	8,2%	26
mAb410.30F305	1	VH1-12-9	5	5,1%	52
EV1-15	1	VH1-12-8	10	10,2%	78
mAb112	1	VH1-12-1	11	11,2%	71
EU	1	VH1-12-1	11	11,2%	28
H210	1	VH1-12-1	12	12,2%	66
TRANSGENE	1	VH1-12-1	0	0,0%	111
CLL2-1	1	VH1-12-1	0	0,0%	30
CLL10 13-3	1	VH1-12-1	0	0,0%	29
LS7	1	VH1-12-7	4	4,1%	113
ALL7-1	1	VH1-12-7	0	0,0%	30
CLL3-1	1	VH1-12-7	1	1,0%	30
ALL56-1	1	VH1-12-8	0	0,0%	30
ALL1-1	1	VH1-12-6	1	1,0%	30
ALL4-1	1	VH1-12-8	0	0,0%	30

Table 2C: (continued)

Name ¹	age ²	Assigned family ³	Gene name ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
ALL56 15-4	8	1	VH1-12-3	5	5,1%	29
CLL4-1	8	1	VH1-12-1	1	1,0%	30
Au92.1	9	1	VH1-12-5	0	0,0%	49
RF-TS3	10	1	VH1-12-5	1	1,0%	82
Au4.1	9	1	VH1-12-5	1	1,0%	49
HP1	10	1	VH1-12-3	13	13,3%	110
BLI	12	1	VH1-12-5	5	5,1%	72
No.13	10	1	VH1-12-2	19	19,4%	76
TR1.23	11	1	VH1-12-2	23	23,5%	88
S1-1	12	1	VH1-12-2	18	18,4%	76
TR1.10	10	1	VH1-12-12	14	14,3%	88
E55 1.A2	10	1	VH1-12-15	3	3,1%	26
SP2	1	1	VH1-12-3	15	15,3%	89
TNF-H9G1	1	1	VH1-12-3	2	2,0%	42
G3D10H	1	1	VH1-12-5	19	19,4%	127
TR1.9	1	1	VH1-12-2	14	14,3%	88
TR1.8	1	1	VH1-12-1	24	24,5%	88
LUNm01	1	1	VH1-12-5	22	22,4%	9
K1B12H	1	1	VH1-12-7	23	23,5%	127
L3B2	9	1	VH1-12-6	2	2,0%	46
ss2	1	1	VH1-12-6	2	2,0%	46
No.86	1	1	VH1-12-1	20	20,4%	76
TR1.6	1	1	VH1-12-1	19	19,4%	88
ss7	9	1	VH1-12-7	3	3,1%	46
s5B7	1	1	VH1-12-1	0	0,0%	46
s6A3	9	1	VH1-12-1	0	0,0%	46
ss6	9	1	VH1-12-1	0	0,0%	46
L2H7	1	1	VH1-12-12	0	0,0%	46
s6BG8	9	1	VH1-12-12	0	0,0%	46
s6C9	1	1	VH1-12-12	0	0,0%	46
HIV-b4	1	1	VH1-12-12	21	21,4%	12
HIV-b12	1	1	VH1-12-12	21	21,4%	12
L3G5	1	1	VH1-12-5	1	1,0%	46
22	1	1	VH1-12-5	11	11,2%	118
L2A12	1	1	VH1-12-15	3	3,1%	46
PHOX15	1	1	VH1-12-7	20	20,4%	73

Table 2C: (continued)

Name ¹	Imputed family ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
LUNm03	1	VH1-1X-1	18	18,4%	9
CEA4-8A	1	VH1-12-7	1	1,0%	42
M60	1	VH2-31-3	3	3,0%	103
HiH10	1	VH2-31-5	9	9,0%	4
COR	1	VH2-31-2	11	11,0%	91
2-115-19	1	VH2-31-11	8	8,1%	124
OU	1	VH2-31-14	20	25,6%	92
HE	1	VH2-31-13	19	19,0%	27
CLL33 40-1	1	VH2-31-5	2	2,0%	29
E55 3.9	1	VH2-31-5	7	7,2%	26
MTFC3	1	VH2-31-4	21	21,0%	131
MTFC11	1	VH2-31-4	21	21,0%	131
MTFJ1	1	VH2-31-4	21	21,0%	131
MTFJ2	1	VH2-31-4	21	21,0%	131
MTFUJ4	1	VH2-31-4	21	21,0%	131
MTFUJ5	1	VH2-31-4	21	21,0%	131
MTFUJ2	1	VH2-31-4	22	22,0%	131
MTFC8	1	VH2-31-4	23	23,0%	131
TD e Vq	1	VH2-31-4	0	0,0%	16
rMTF	1	VH2-31-4	5	5,0%	131
MTFUJ6	1	VH2-31-4	10	10,0%	131
RF-KES	1	VH2-31-4	9	9,0%	85
N51P8	1	VH2-31-1	9	9,0%	77
TEI	1	VH2-31-8	21	21,4%	20
33.H11	1	VH2-31-9	10	10,2%	129
SB1/D8	1	VH2-31-3	14	14,0%	2
38P1	1	VH2-31-3	0	0,0%	104
BRO'IGM	1	VH2-31-3	13	13,4%	19
NIE	1	VH2-31-7	15	15,3%	87
3D6	1	VH2-31-6	5	5,1%	35
ZM1-1	1	VH2-31-3	8	8,2%	5
E55 3.15	1	VH2-31-5	0	0,0%	26
gF9	1	VH2-31-3	15	15,3%	75
THY-32	1	VH2-31-6	3	3,1%	42
RF-KL5	1	VH2-31-6	5	5,1%	96
OST577	1	VH2-31-3	6	6,1%	5

Table 2C: (continued)

Name ¹	puted mily ³	line g ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
BO	3	VH-12-19	15	15,3%	10
TT125	3	VH-13-10	15	15,3%	64
2-115-58	3	VH-13-10	11	11,2%	124
KOL	3	VH-12-14	16	16,3%	102
mAb60	3	VH-12-17	14	14,3%	45
RF-AN	3	VH-12-06	8	8,2%	85
BUT	3	VH-12-06	13	13,4%	119
KOL-based CAMPATH-9	3	VH-12-13	16	16,3%	41
B1	3	VH-12-19	13	13,3%	53
N98P1	3	VH-12-01	13	13,3%	77
TT117	3	VH-12-10	12	12,2%	64
WEA	3	VH-12-12	15	15,3%	40
HIL	3	VH-12-14	14	14,3%	23
s5A10	3	VH-12-14	0	0,0%	46
s5D11	3	VH-12-07	0	0,0%	46
s6C8	3	VH-12-07	0	0,0%	46
s6H12	3	VH-12-07	0	0,0%	46
VH10.7	3	VH-12-14	16	16,3%	128
HIV-loop2	3	VH-12-07	16	16,3%	12
HIV-loop35	3	VH-12-07	16	16,3%	12
TRO	3	VH-12-01	13	13,3%	61
SA-4B	3	VH-12-01	15	15,3%	125
L2B5	3	VH-12-13	0	0,0%	46
s6E11	3	VH-12-13	0	0,0%	46
s6H7	3	VH-12-13	0	0,0%	46
ss1	3	VH-12-13	0	0,0%	46
ss8	3	VH-12-13	0	0,0%	46
DOB	3	VH-12-16	21	21,4%	116
THY-33	3	VH-12-15	20	20,4%	42
NOV	3	VH-12-19	14	14,3%	38
rsv13H	3	VH-12-24	20	20,4%	11
L3G11	3	VH-12-20	2	2,0%	46
L2E8	3	VH-12-19	0	0,0%	46
L2D10	3	VH-12-10	1	1,0%	46
L2E7	3	VH-12-10	1	1,0%	46

Table 2C: (continued)

Name ¹	a	puted family ³	germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
L3A10	1	3	VH3-13-24	0	0,0%	46
L2E5	9	3	VH3-13-2	1	1,0%	46
BUR	11	3	VH3-13-7	21	21,4%	67
s4D5	11	3	VH3-11-3	1	1,0%	46
19	1	3	VH3-13-16	4	4,1%	118
s5D4	9	3	VH3-13-1	0	0,0%	46
s6A8	11	3	VH3-13-1	0	0,0%	46
HIV-loop13	11	3	VH3-13-12	17	17,3%	12
TR1.32	1	3	VH3-11-8	18	18,6%	88
L2B10	9	3	VH3-11-3	1	1,0%	46
TR1.5	1	3	VH3-11-8	21	21,6%	88
s6H9	1	3	VH3-13-25	0	0,0%	46
8	1	3	VH3-13-1	6	6,1%	118
23	1	3	VH3-13-1	6	6,1%	118
7	1	3	VH3-13-1	4	4,1%	118
TR1.3	1	3	VH3-11-8	20	20,6%	88
18/2	1	3	VH3-13-10	0	0,0%	32
18/9	1	3	VH3-13-10	0	0,0%	31
30P1	1	3	VH3-13-10	0	0,0%	106
HF2-1/17	1	3	VH3-13-10	0	0,0%	8
A77	1	3	VH3-13-10	0	0,0%	44
B19.7	1	3	VH3-13-10	0	0,0%	44
M43	1	3	VH3-13-10	0	0,0%	103
1/17	1	3	VH3-13-10	0	0,0%	31
18/17	1	3	VH3-13-10	0	0,0%	31
E54 3.4	1	3	VH3-13-10	0	0,0%	26
LAMBDA-VH26	9	3	VH3-13-10	1	1,0%	95
E54 3.8	1	3	VH3-13-10	1	1,0%	26
GL16	1	3	VH3-13-10	1	1,0%	44
4G12	1	3	VH3-13-10	1	1,0%	56
A73	1	3	VH3-13-10	2	2,0%	44
AL1.3	1	3	VH3-13-10	3	3,1%	117
3.A290	1	3	VH3-13-10	2	2,0%	108
Ab18	1	3	VH3-13-3	2	2,0%	100
E54 3.3	1	3	VH3-13-10	3	3,1%	26
35G6	1	3	VH3-13-10	3	3,1%	57

Table 2C: (continued)

Name ¹	aa ²	puted mily ³	line ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
A95	107	3	VH3-10	5	5,1%	44
Ab25	128	3	VH3-10	5	5,1%	100
N87	126	3	VH3-10	4	4,1%	77
ED8.4	99	3	VH3-10	6	6,1%	2
RF-KL1	122	3	VH3-10	6	6,1%	82
AL1.1	111	3	VH3-10	2	2,0%	117
AL3.11	102	3	VH3-10	1	1,0%	117
32.B9	127	3	VH3-8	6	6,1%	129
TK1	101	3	VH3-10	2	2,0%	117
POP	121	3	VH3-10	8	8,2%	115
9F2H	121	3	VH3-10	9	9,2%	127
VD	111	3	VH3-10	9	9,2%	10
Vh38Cl.10	121	3	VH3-10	8	8,2%	74
Vh38Cl.9	121	3	VH3-10	8	8,2%	74
Vh38Cl.8	121	3	VH3-10	8	8,2%	74
63P1	101	3	VH3-8	0	0,0%	104
60P2	101	3	VH3-8	0	0,0%	104
AL3.5	99	3	VH3-10	2	2,0%	117
GF4/1.1	111	3	VH3-10	10	10,2%	39
Ab21	121	3	VH3-10	12	12,2%	100
TD d Vp	101	3	VH3-17	2	2,0%	16
Vh38Cl.4	121	3	VH3-10	8	8,2%	74
Vh38Cl.5	121	3	VH3-10	8	8,2%	74
AL3.4	101	3	VH3-10	1	1,0%	117
FOG1-A3	101	3	VH3-19	2	2,0%	42
HA3D1	101	3	VH3-21	1	1,0%	81
E54 3.2	101	3	VH3-24	0	0,0%	26
mAb52	128	3	VH3-12	2	2,0%	51
mAb53	128	3	VH3-12	2	2,0%	51
mAb56	128	3	VH3-12	2	2,0%	51
mAb57	128	3	VH3-12	2	2,0%	51
mAb58	128	3	VH3-12	2	2,0%	51
mAb59	128	3	VH3-12	2	2,0%	51
mAb105	128	3	VH3-12	2	2,0%	51
mAb107	128	3	VH3-12	2	2,0%	51
E55 3.14	110	3	VH3-19	0	0,0%	26

Table 2C: (continued)

Name ¹	aa ²	puted mily ³	C. line gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
F13-28	106	3	VH3-13-19	1	1,0%	94
mAb55	127	3	VH3-13-18	4	4,1%	51
YSE	117	3	VH3-13-24	6	6,1%	72
E55 3.23	106	3	VH3-13-19	2	2,0%	26
RF-TS5	101	3	VH3-13-1	3	3,1%	85
N42P5	124	3	VH3-13-2	7	7,1%	77
FOG1-H6	110	3	VH3-13-16	7	7,1%	42
O-81	115	3	VH3-13-19	11	11,2%	47
HIV-s8	122	3	VH3-13-12	11	11,2%	12
mAb114	125	3	VH3-13-19	12	12,2%	71
33.F12	116	3	VH3-13-2	4	4,1%	129
4B4	119	3	VH3-13-3	0	0,0%	101
M26	123	3	VH3-13-3	0	0,0%	103
VHGL 3.1	100	3	VH3-13-3	0	0,0%	26
E55 3.13	113	3	VH3-13-3	1	1,0%	26
SB5/D6	101	3	VH3-13-6	3	3,0%	2
RAY4	101	3	VH3-13-6	3	3,0%	2
82-D V-D	100	3	VH3-13-3	5	5,0%	112
MAL	113	3	VH3-13-3	5	5,0%	72
LOC	113	3	VH3-13-6	5	5,0%	72
LSF2	111	3	VH3-13-6	11	11,0%	2
HIB RC3	100	3	VH3-13-6	11	11,0%	1
56P1	100	3	VH3-13-7	0	0,0%	104
M72	102	3	VH3-13-7	0	0,0%	103
M74	101	3	VH3-13-7	0	0,0%	103
E54 3.5	100	3	VH3-13-7	0	0,0%	26
2E7	100	3	VH3-13-7	0	0,0%	63
2P1	100	3	VH3-13-7	0	0,0%	104
RF-SJ2	100	3	VH3-13-7	1	1,0%	83
PR-TS1	100	3	VH3-13-7	1	1,0%	85
KIM46H	100	3	VH3-13-13	0	0,0%	18
E55 3.6	100	3	VH3-13-7	2	2,0%	26
E55 3.10	100	3	VH3-13-13	1	1,0%	26
3.B6	100	3	VH3-13-13	1	1,0%	108
E54 3.6	100	3	VH3-13-13	1	1,0%	26
FL2-2	100	3	VH3-13-13	1	1,0%	80

Table 2C: (continued)

Name ¹	aa ²	uted ily ³	C e ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
RF-SJ3	112	3	VH-13-7	2	2,0%	85
E55 3.5	105	3	VH-13-14	1	1,0%	26
BSA3	121	3	VH-13-13	1	1,0%	73
HMST-1	119	3	VH-13-7	3	3,1%	130
RF-TS2	120	3	VH-13-13	4	4,1%	82
E55 3.12	10	3	VH-15	0	0,0%	26
19.E7	120	3	VH-14	3	3,1%	129
11-50	119	3	VH-13	6	6,1%	130
E29.1	12	3	VH-15	2	2,0%	25
E55 3.16	10	3	VH-7	6	6,1%	26
TNF-E1	117	3	VH-7	7	7,1%	42
RF-SJ1	127	3	VH-13	6	6,1%	83
FOG1-A4	1	3	VH-7	8	8,2%	42
TNF-A1	1	3	VH-15	4	4,1%	42
PR-SJ2	10	3	VH-14	8	8,2%	85
HN.14	1	3	VH-13	10	10,2%	33
CAM	1	3	VH-7	12	12,2%	65
HIV-B8	1	3	VH-7	9	9,2%	12
HIV-b27	1	3	VH-7	9	9,2%	12
HIV-b8	1	3	VH-7	9	9,2%	12
HIV-s4	1	3	VH-7	9	9,2%	12
HIV-B26	1	3	VH-7	9	9,2%	12
HIV-B35	1	3	VH-7	10	10,2%	12
HIV-b18	1	3	VH-7	10	10,2%	12
HIV-b22	1	3	VH-7	11	11,2%	12
HIV-b13	1	3	VH-7	12	12,2%	12
333	1	3	VH-4	24	24,0%	24
1H1	1	3	VH-4	24	24,0%	24
1B11	1	3	VH-4	23	23,0%	24
CLL30 2-3	1	3	VH-19	1	1,0%	29
GA	1	3	VH-7	19	19,4%	36
JeB	1	3	VH-14	3	3,1%	7
GAL	1	3	VH-9	10	10,2%	126
K6H6	1	3	VH-6	18	18,0%	60
K4B8	1	3	VH-6	18	18,0%	60
K5B8	1	3	VH-6	18	18,0%	60

Table 2C: (continued)

Name ¹	a ²	puted family ³	line e ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
K5C7	11	3	VH1-1X-6	19	19,0%	60
K5G5	11	3	VH2-1X-6	19	19,0%	60
K6F5	11	3	VH3-1X-6	19	19,0%	60
AL3.16	9	3	VH2-13-10	1	1,0%	117
N86P2	9	3	VH2-13-10	3	3,1%	77
N54P6	9	3	VH2-13-16	7	7,1%	77
LAMBDA HT112-1	11	4	VH1-1-2	0	0,0%	3
HY18	11	4	VH1-1-2	0	0,0%	43
mAb63	11	4	VH1-1-2	0	0,0%	45
FS-3	11	4	VH1-1-2	0	0,0%	86
FS-5	11	4	VH1-1-2	0	0,0%	86
FS-7	11	4	VH1-1-2	0	0,0%	86
FS-8	11	4	VH1-1-2	0	0,0%	86
PR-TS2	1	4	VH1-1-2	0	0,0%	85
RF-TMC	1	4	VH1-1-2	0	0,0%	85
mAb216	1	4	VH1-1-2	1	1,0%	15
mAb410.7.F91	1	4	VH1-1-2	1	1,0%	52
mAbA6H4C5	11	4	VH1-1-2	1	1,0%	15
Ab44	11	4	VH1-1-2	2	2,1%	100
6H-3C4	11	4	VH1-1-2	3	3,1%	59
FS-6	1	4	VH1-1-2	6	6,2%	86
FS-2	1	4	VH1-1-2	6	6,2%	84
HIG1	11	4	VH1-1-2	7	7,2%	62
FS-4	1	4	VH1-1-2	8	8,2%	86
SA-4A	1	4	VH1-1-2	9	9,3%	125
LES-C	1	4	VH1-1-2	10	10,3%	99
DI	7	4	VH1-1-2	16	16,5%	58
Ab26	1	4	VH1-1-4	8	8,1%	100
TS2	1	4	VH1-1-2	15	15,2%	110
265-695	1	4	VH1-1-2	16	16,5%	5
WAH	1	4	VH1-1-3	19	19,2%	93
268-D	1	4	VH1-1-3	22	22,7%	6
58P2	1	4	VH1-1-3	0	0,0%	104
mAb67	1	4	VH1-1-3	1	1,0%	45
4.L39	1	4	VH1-1-3	2	2,1%	108
mF7	1	4	VH1-1-3	3	3,0%	75

Table 2C: (continued)

Name ¹	aa ²	mutated residues ³	C ⁴	Δ	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
33.C9	127	4	VH	-5	7	7,1%	129
Pag-1	128	4	VH	-16	5	5,2%	50
B3	128	4	VH	-3	8	8,2%	53
IC4	129	4	VH	-8	6	6,2%	70
C6B2	127	4	VH	-12	4	4,0%	48
N78	11	4	VL	3	11	11,3%	77
B2	10	4	VL	3	12	12,4%	53
WRD2	127	4	VH	12	6	6,2%	90
mAb426.4.2F20	12	4	VL	3	2	2,1%	52
E54 4.58	11	4	VL	3	1	1,0%	26
WRD6	12	4	VL	12	10	10,3%	90
mAb426.12.3F1.4	12	4	VL	3	4	4,1%	52
E54 4.2	11	4	VL	3	2	2,0%	26
WIL	11	4	VL	3	0	0,0%	90
COF	12	4	VL	3	0	0,0%	90
LAR	12	4	VL	3	2	2,0%	90
WAT	12	4	VL	3	4	4,0%	90
mAb61	11	4	VL	3	5	5,1%	45
WAG	11	4	VL	3	0	0,0%	90
RF-SJ4	11	4	VL	12	2	2,0%	85
E54 4.4	11	4	VL	3	0	0,0%	26
E55 4.A1	11	4	VL	3	0	0,0%	26
PR-SJ1	11	4	VL	3	1	1,0%	85
E54 4.23	11	4	VL	3	1	1,0%	26
CLL7 7-2	9	4	VL	12	0	0,0%	29
37P1	9	4	VL	12	0	0,0%	104
ALL52 30-2	9	4	VL	12	4	4,0%	29
EBV-21	9	5	VL	1	0	0,0%	13
CB-4	9	5	VL	1	0	0,0%	13
CLL-12	9	5	VL	1	0	0,0%	13
L3-4	9	5	VL	1	0	0,0%	13
CLL11	9	5	VL	1	0	0,0%	17
CORD3	9	5	VL	1	0	0,0%	17
CORD4	9	5	VL	1	0	0,0%	17
CORD8	9	5	VL	1	0	0,0%	17
CORD9	9	5	VL	1	0	0,0%	17

Table 2C: (continued)

Name ¹	aa ²	puted mily ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
CD+1	98	5	VH5-12-1	0	0,0%	17
CD+3	98	5	VH5-12-1	0	0,0%	17
CD+4	98	5	VH5-12-1	0	0,0%	17
CD-1	98	5	VH5-12-1	0	0,0%	17
CD-5	98	5	VH5-12-1	0	0,0%	17
VERG14	98	5	VH5-12-1	0	0,0%	17
PBL1	98	5	VH5-12-1	0	0,0%	17
PBL10	98	5	VH5-12-1	0	0,0%	17
STRAb SA-1A	127	5	VH5-12-1	0	0,0%	125
DOB ¹	127	5	VH5-12-1	0	0,0%	97
VERG5	98	5	VH5-12-1	0	0,0%	17
PBL2	98	5	VH5-12-1	1	1,0%	17
Tu16	111	5	VH5-12-1	1	1,0%	49
PBL12	98	5	VH5-12-1	1	1,0%	17
CD+2	98	5	VH5-12-1	1	1,0%	17
CORD10	98	5	VH5-12-1	1	1,0%	17
PBL9	98	5	VH5-12-1	1	1,0%	17
CORD2	98	5	VH5-12-1	2	2,0%	17
PBL6	98	5	VH5-12-1	2	2,0%	17
CORD5	98	5	VH5-12-1	2	2,0%	17
CD-2	98	5	VH5-12-1	2	2,0%	17
CORD1	98	5	VH5-12-1	2	2,0%	17
CD-3	98	5	VH5-12-1	3	3,1%	17
VERG4	98	5	VH5-12-1	3	3,1%	17
PBL13	98	5	VH5-12-1	3	3,1%	17
PBL7	98	5	VH5-12-1	3	3,1%	17
HAN	1	5	VH5-12-1	3	3,1%	97
VERG3	98	5	VH5-12-1	3	3,1%	17
PBL3	98	5	VH5-12-1	3	3,1%	17
VERG7	98	5	VH5-12-1	3	3,1%	17
PBL5	98	5	VH5-12-1	0	0,0%	17
CD-4	98	5	VH5-12-1	4	4,1%	17
CLL10	98	5	VH5-12-1	4	4,1%	17
PBL11	98	5	VH5-12-1	4	4,1%	17
CORD6	98	5	VH5-12-1	4	4,1%	17
VERG2	98	5	VH5-12-1	5	5,1%	17

Table 2C: (continued)

Name ¹	aa ²	puted ily ³	Online gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
83P2	11	5	VH5-12-1	0	0,0%	103
VERG9	98	5	VH5-12-1	6	6,1%	17
CLL6	98	5	VH5-12-1	6	6,1%	17
PBL8	98	5	VH5-12-1	7	7,1%	17
Ab2022	120	5	VH5-12-1	3	3,1%	100
CAV	12	5	VH5-12-4	0	0,0%	97
HOW	12	5	VH5-12-4	0	0,0%	97
PET	12	5	VH5-12-4	0	0,0%	97
ANG	12	5	VH5-12-4	0	0,0%	97
KER	12	5	VH5-12-4	0	0,0%	97
5.M13	11	5	VH5-12-4	0	0,0%	107
Au2.1	11	5	VH5-12-4	1	1,0%	49
WS1	11	5	VH5-12-1	9	9,2%	110
TD Vn	9	5	VH5-12-4	1	1,2%	16
TEL13	11	5	VH5-12-1	9	9,2%	73
E55 5.237	11	5	VH5-12-4	2	2,0%	26
VERG1	9	5	VH5-12-1	10	10,2%	17
CD4-74	11	5	VH5-12-1	10	10,2%	42
257-D	11	5	VH5-12-1	11	11,2%	6
CLL4	9	5	VH5-12-1	11	11,2%	17
CLL8	9	5	VH5-12-1	11	11,2%	17
Ab2	11	5	VH5-12-1	12	12,2%	120
Vh383ex	9	5	VH5-12-1	12	12,2%	120
CLL3	9	5	VH5-12-2	11	11,2%	17
Au59.1	11	5	VH5-12-1	12	12,2%	49
TEL16	11	5	VH5-12-1	12	12,2%	73
M61	11	5	VH5-12-1	0	0,0%	103
Tu0	9	5	VH5-12-1	5	5,0%	49
P2-51	11	5	VH5-12-1	13	12,2%	121
P2-54	11	5	VH5-12-1	11	11,2%	121
P1-56	11	5	VH5-12-1	3	3,0%	121
P2-53	11	5	VH5-12-1	10	11,2%	121
P1-51	12	5	VH5-12-1	19	15,8%	121
P1-54	12	5	VH5-12-1	3	3,0%	121
P3-69	11	5	VH5-12-1	4	4,0%	121
P3-9	11	5	VH5-12-1	4	4,0%	121

Table 2C: (continued)

Name ¹	aa ²	puted mily ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
1-185-37	125	5	VH5-12-4	0	0,0%	124
1-187-29	125	5	VH5-12-4	0	0,0%	124
P1-58	128	5	VH5-12-4	10	10,2%	121
P2-57	119	5	VH5-12-4	3	3,1%	121
P2-55	119	5	VH5-12-1	5	5,1%	121
P2-56	113	5	VH5-12-1	20	20,4%	121
P2-52	122	5	VH5-12-1	11	11,2%	121
P3-60	122	5	VH5-12-1	8	8,2%	121
P1-57	113	5	VH5-12-1	4	4,1%	121
P1-55	112	5	VH5-12-1	14	14,3%	121
MD3-4	113	5	VH5-12-4	12	12,2%	5
P1-52	111	5	VH5-12-1	11	11,2%	121
CLL5	9	5	VH5-12-1	13	13,3%	17
CLL7	9	5	VH5-12-1	14	14,3%	17
L2F10	113	5	VH5-12-1	1	1,0%	46
L3B6	9	5	VH5-12-1	1	1,0%	46
VH6.A12	113	6	VH6-35-1	13	12,9%	122
s5A9	113	6	VH6-35-1	1	1,0%	46
s6G4	9	6	VH6-35-1	1	1,0%	46
ss3	9	6	VH6-35-1	1	1,0%	46
6-1G1	113	6	VH6-35-1	0	0,0%	14
F19L16	113	6	VH6-35-1	0	0,0%	68
L16	113	6	VH6-35-1	0	0,0%	69
M71	113	6	VH6-35-1	0	0,0%	103
ML1	113	6	VH6-35-1	0	0,0%	69
F19ML1	113	6	VH6-35-1	0	0,0%	68
15P1	113	6	VH6-35-1	0	0,0%	104
VH6.N1	113	6	VH6-35-1	0	0,0%	122
VH6.N11	113	6	VH6-35-1	0	0,0%	122
VH6.N12	113	6	VH6-35-1	0	0,0%	122
VH6.N2	113	6	VH6-35-1	0	0,0%	122
VH6.N5	113	6	VH6-35-1	0	0,0%	122
VH6.N6	113	6	VH6-35-1	0	0,0%	122
VH6.N7	113	6	VH6-35-1	0	0,0%	122
VH6.N8	113	6	VH6-35-1	0	0,0%	122
VH6.N9	113	6	VH6-35-1	0	0,0%	122

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Table 2C: (continued)

Name ¹	aa ²	puted sily ³	Germline gene ⁴	Diff. to germline ⁵	% diff. to germline ⁶	Reference ⁷
VH6.N10	123	5	VH6-35-1	0	0,0%	122
VH6.A3	123	5	VH6-35-1	0	0,0%	122
VH6.A1	124	5	VH6-35-1	0	0,0%	122
VH6.A4	120	5	VH6-35-1	0	0,0%	122
E55 6.16	116	5	VH6-35-1	0	0,0%	26
E55 6.17	120	5	VH6-35-1	0	0,0%	26
E55 6.6	120	5	VH6-35-1	0	0,0%	26
VHGL 6.3	102	5	VH6-35-1	0	0,0%	26
CB-201	110	5	VH6-35-1	0	0,0%	109
VH6.N4	122	5	VH6-35-1	0	0,0%	122
E54 6.4	109	5	VH6-35-1	1	1,0%	26
VH6.A6	120	5	VH6-35-1	1	1,0%	122
E55 6.14	120	5	VH6-35-1	1	1,0%	26
E54 6.6	109	5	VH6-35-1	1	1,0%	26
E55 6.10	111	5	VH6-35-1	1	1,0%	26
E54 6.1	109	5	VH6-35-1	2	2,0%	26
E55 6.13	111	5	VH6-35-1	2	2,0%	26
E55 6.3	111	5	VH6-35-1	2	2,0%	26
E55 6.7	111	5	VH6-35-1	2	2,0%	26
E55 6.2	111	5	VH6-35-1	2	2,0%	26
E55 6.X	111	5	VH6-35-1	2	2,0%	26
E55 6.11	111	5	VH6-35-1	3	3,0%	26
VH6.A11	111	5	VH6-35-1	3	3,0%	122
A10	111	5	VH6-35-1	3	3,0%	68
E55 6.1	111	5	VH6-35-1	4	4,0%	26
FK-001	111	5	VH6-35-1	4	4,0%	65
VH6.A5	111	5	VH6-35-1	4	4,0%	122
VH6.A7	111	5	VH6-35-1	4	4,0%	122
HBp2	111	5	VH6-35-1	4	4,0%	4
Au46.2	111	5	VH6-35-1	5	5,0%	49
A431	111	5	VH6-35-1	5	5,0%	68
VH6.A2	111	5	VH6-35-1	5	5,0%	122
VH6.A9	111	5	VH6-35-1	8	7,0%	122
VH6.A8	111	5	VH6-35-1	10	9,0%	122
VH6-FF3	111	5	VH6-35-1	12	11,0%	123
VH6.A10	111	5	VH6-35-1	12	11,0%	122

Table 2C: (continued)

Name ¹	aa ²	puted nily ³	Germlin gene ⁴	f. to line ⁵	% diff. to germlin ⁶	Reference ⁷
VH6-EB10	117	6	VH6-35-1	3	3,0%	123
VH6-E6	119	6	VH6-35-1	6	5,9%	123
VH6-FE2	121	6	VH6-35-1	6	5,9%	123
VH6-EE6	116	6	VH6-35-1	6	5,9%	123
VH6-FD10	118	6	VH6-35-1	6	5,9%	123
VH6-EX8	117	6	VH6-35-1	6	5,9%	123
VH6-FG9	121	6	VH6-35-1	6	7,9%	123
VH6-E5	116	6	VH6-35-1	3	8,9%	123
VH6-EC8	12	6	VH6-35-1	3	8,9%	123
VH6-E10	12	6	VH6-35-1	10	9,9%	123
VH6-FF11	123	6	VH6-35-1	11	10,9%	123
VH6-FD2	115	6	VH6-35-1	11	10,9%	123
CLL10 17-2	85	6	VH6-35-1	4	4,0%	29
VH6-BB11	94	6	VH6-35-1	4	4,0%	123
VH6-B4I	93	6	VH6-35-1	7	6,9%	123
JU17	107	6	VH6-35-1	3	3,0%	114
VH6-BD9	9	6	VH6-35-1	11	10,9%	123
VH6-BB9	9	6	VH6-35-1	2	11,9%	123

Table 3A: assignment of rearranged V kappa sequences to their germline counterparts

Family ¹	Name	Re	ed ²	Sum
1	Vk1-1			
1	Vk1-2			
1	Vk1-3			
1	Vk1-4			
1	Vk1-5			
1	Vk1-6			
1	Vk1-7			
1	Vk1-8			
1	Vk1-9			
1	Vk1-10			
1	Vk1-11			
1	Vk1-12			
1	Vk1-13			
1	Vk1-14			
1	Vk1-15			
1	Vk1-16			
1	Vk1-17			
1	Vk1-18			
1	Vk1-19			
1	Vk1-20			
1	Vk1-21			
1	Vk1-22			
1	Vk1-23			
				<i>119 entries</i>
2	Vk2-1			
2	Vk2-2			
2	Vk2-3			
2	Vk2-4			
2	Vk2-5			
2	Vk2-6			
2	Vk2-7			
2	Vk2-8			
2	Vk2-9			
2	Vk2-10			
2	Vk2-11			
2	Vk2-12			
				<i>25 entries</i>
3	Vk3-1			
3	Vk3-2			

Table 3A: (continued)

Family ¹	Name	Re	ged ²	Sum
3	Vk3-3			
3	Vk3-4	5		
3	Vk3-5			
3	Vk3-6			
3	Vk3-7			
3	Vk3-8	0		192 entries
4	Vk4-1			33
5	Vk5-1			1
6	Vk6-1			
6	Vk6-2			0 entries
7	Vk7-1			0 entries

86

Table 3B: assignment of rearranged V lambda sequences to their germline counterparts

Family ¹	Name	Rearranged ²	Sum
1	DPL1	1	
1	DPL2	14	
1	DPL3	6	
1	DPL4	1	
1	HUMLV117	4	
1	DPL5	13	
1	DPL6	0	
1	DPL7	0	
1	DPL8	3	
1	DPL9	0	42 entries
2	DPL10	5	
2	VLAM3DA 2.1	0	
2	DPL11	23	
2	DPL12	15	
2	DPL13	0	
2	DPL14	0	43 entries
3	DPL16	10	
3	DPL23	19	
3	Humlv318	9	38 entries
7	DPL18	1	
7	DPL19	0	1 entries
8	DPL21	2	
8	HUMLV801	6	8 entries
9	DPL22	0	
unassigned	DPL24	0	
10	gVL 20.4	0	

Table 3C: assignment of rearranged V heavy chain sequences to their germline counterparts

Family ¹	Name	Rearranged ²
1	VH1-12-1	38
1	VH1-12-8	2
1	VH1-12-2	2
1	VH1-12-9	2
1	VH1-12-3	0
1	VH1-12-4	0
1	VH1-12-5	3
1	VH1-12-6	0
1	VH1-12-7	23
1	VH1-13-1	1
1	VH1-13-2	1
1	VH1-13-3	0
1	VH1-13-4	0
1	VH1-13-5	0
1	VH1-13-6	17
1	VH1-13-7	0
1	VH1-13-8	3
1	VH1-13-9	0
1	VH1-13-10	0
1	VH1-13-11	0
1	VH1-13-12	10
1	VH1-13-13	0
1	VH1-13-14	0
1	VH1-13-15	4
1	VH1-13-16	2
1	VH1-13-17	0
1	VH1-13-18	1
1	VH1-13-19	0
1	VH1-13-20	1
<hr/>		
2	VH2-21-1	1
2	VH2-21-2	0
2	VH2-21-3	1
2	VH2-21-4	1
2	VH2-21-5	0
2	VH2-21-6	2
2	VH2-21-7	0
2	VH2-21-8	0
<hr/>		
119 entries		

Table 3C: (continued)

Family ¹	Name	F. arranged ²	cm
2	VH2-31-14	1	
2	VH2-31-8	0	
2	VH2-31-9	0	
2	VH2-31-10	0	
2	VH2-31-11	1	
2	VH2-31-12	0	
2	VH2-31-13	1	7 entries
3	VH3-11-	0	
3	VH3-11-	0	
3	VH3-11-	5	
3	VH3-11-4	0	
3	VH3-11-5	1	
3	VH3-11-6	1	
3	VH3-11-7	0	
3	VH3-11-8	5	
3	VH3-11-9	3	
3	VH3-11-10	3	
3	VH3-11-11	0	
3	VH3-11-12	0	
3	VH3-11-13	0	
3	VH3-11-14	0	
3	VH3-11-15	0	
3	VH3-11-16	0	
3	VH3-11-17	12	
3	VH3-11-18	4	
3	VH3-11-19	0	
3	VH3-11-20	46	
3	VH3-11-21	0	
3	VH3-11-22	11	
3	VH3-11-23	17	
3	VH3-11-24	3	
3	VH3-11-25	4	
3	VH3-11-26	3	
3	VH3-11-27	2	
3	VH3-11-28	1	
3	VH3-11-29	13	
3	VH3-11-30	1	
3	VH3-11-31	1	
3	VH3-11-32	0	

Table 3C: (continued)

4.

57 entries

Table 4A: Analysis of V kappa group 1

amino acid ¹	Framework I															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A													102		1	
B						1										
C														1		
D																
E															1	
F										6				1		
G																105
H																
I															4	
K																
L											96		1			
M																
N																
P										1		2			1	
Q						88					1					
R																
S										30		103		103		
T						88				8						
V											8		2		98	
W																
X																
Y																
-																
unknown																
not sequenc					17	16										
sum of s					88	89				105	105	105	105	105	105	105
oomca					88	88				96	103	102	103		98	105
mcaa ²					T	Q				L	S	A	S	V	G	
rel. oomc					100%	99%				91%	98%	97%	98%	93%	100%	
pos occu					1	2				3	2	3	3	5	1	

Table 4A: Analysis of V kappa sequences

amino acid ¹	21	22	23	27	A	B	C	D
A		1						
B				1				
C								
D								
E				2				
F	2							
G								
H				1				
I	101	1						
K				1				
L								
M								
N				1				
P								
Q				100				
R								
S				2				
T		10		1				
V	2							
W								
X								
Y								
-								
unknown (?)					105	105	105	105
not sequenced								
sum of seq ²	105	10	5	105	105	105	105	105
oomcaa ³	101	10	2	100	105	105	105	105
mcaa ⁴	1	1		Q	-	-	-	-
rel. oomcaa ⁵	96%	100%		95%	100%	100%	100%	100%
pos occupied ⁶	3		1	5	1	1	1	1

Table 4A: Analysis of V kappa 1

amino acid ¹	E	CIR					
		30	31	32	33	34	35
A		1					
B						1	1
C							
D		1				1	
E						2	
F		1				6	
G		7					
H		1				2	
I		1					
K							95
L		2					
M							
N		16					
P							102
Q						98	103
R		16					2
S		57					3
T							1
V		1					
W						104	
X							
Y		1				98	
-							
unknown (?)							3
not sequences						1	1
sum of seq		105	1			104	104
oomcaa ²		57				104	98
mcaa ³		S				W	Y
rel. oomcaa ³		54%				100%	94%
pos occupied		12				1	2

Table 4A: Analysis of M kappa seq 1

amino acid ¹			CDR II					
	45	46	50	51	52	53	54	55
A			50	95				
B								
C								
D			21	1	1	1		
E	1		1		1			33
F					1			
G			9	2				
H								1
I						1		
K	86		16			2		5
L							101	
M								
N	10		2		1	25		
P			1					1
Q	1							62
R	3					1	1	2
S	1		1	1	99	41	2	
T	1		1	4	1	31		
V				1		1		
W								
X	1					1		
Y			1					
-								
unknown								
not sequenced	1		2	1	1	1	1	1
sum of seq	104		103	104	104	104	104	104
omaa ²	86		10	95	99	41	101	62
mcaa ³	K		A	A	S	S	L	Q
rel. comen ⁴	83%		10%	91%	95%	39%	97%	60%
pos occup ⁵	8		10	1	6	9	3	6

Table 4A: Analysis of V kappa subunit in 1

amino acid ¹	55	60	61	62	63	66	67	68	69	70
A	3					2	1	1	1	
B										
C										
D										67
E								1		30
F				1			3			
G						101		102		
H										3
I					3					
K			1							1
L					1					
M									1	
N										
P		2								
Q										
R			10		1	1			2	
S		103			9		100			
T								101		
V										1
W										
Y										
unknown										
not sequenced										
sum of seq ²		105	10	1	9	105	105	105	105	105
total seq ³		103	10	10	9	103	100	102	101	67
no. of ⁴		S	R	F	S	G	S	G	T	D
rel. c ⁵		98%	9%	1%	9%	95%	95%	97%	96%	64%
pos c ⁶		2					4	4	4	7

Table 4A: Analysis of kappa chain region 1

amino acid	75	76	77	78	81	82	83	84	85
A		1			2			101	1
B	1				2				
C									
D		1			16	101			
E					83				
F							73		
G					1			2	
H									
I	99	5					17		
J									
K				10			1		
L									1
M									1
N									1
P									1
Q									
R									
S		8	9				1		
T									97
V	4						11		1
W									
X					1	2			
Y									
unkn									
not se	1	1			2	2	2	2	3
sum	104	10			101	103	103	103	102
oor	99				83	101	73	101	97
m	1				E	D	F	A	T
rel. c	95%				81%	97%	71%	98%	95%
pos c	3	2			2	2	5	2	6

Table 4A: Analysis of Variance for the Kappa subgroup 1

[illegible]

Table 3C: (continued)

Family ¹	Name	Re. arranged ²	Sum
3	VH3-13-23	0	
3	VH3-13-24	4	
3	VH3-13-25	1	
3	VH3-13-26	6	
3	VH3-14-1	1	
3	VH3-14-4	15	
3	VH3-14-2	0	
3	VH3-14-3	0	
3	VH3-1X-1	0	
3	VH3-1X-2	0	
3	VH3-1X-3	6	
3	VH3-1X-4	0	
3	VH3-1X-5	0	
3	VH3-1X-6	11	
3	VH3-1X-7	0	
3	VH3-1X-8	1	
3	VH3-1X-9	0	212 entries
4	VH4-11-1	0	
4	VH4-11-2	20	
4	VH4-11-3	0	
4	VH4-11-4	0	
4	VH4-11-5	0	
4	VH4-11-6	0	
4	VH4-11-7	5	
4	VH4-11-8	7	
4	VH4-11-9	3	
4	VH4-11-10	0	
4	VH4-11-11	0	
4	VH4-11-12	4	
4	VH4-11-13	0	
4	VH4-11-14	0	
4	VH4-11-15	0	
4	VH4-11-16	1	
4	VH4-21-1	0	
4	VH4-21-2	0	
4	VH4-21-3	1	
4	VH4-21-4	1	

Table 3C: (continued)

Family ¹	Name	Unranged ²	Sum
4	VH4-21-5	1	
4	VH4-21-6	1	
4	VH4-21-7	0	
4	VH4-21-8	0	
4	VH4-21-9	0	
4	VH4-31-1	0	
4	VH4-31-2	0	
4	VH4-31-3	0	
4	VH4-31-4	2	
4	VH4-31-5	0	
4	VH4-31-6	0	
4	VH4-31-7	0	
4	VH4-31-8	0	
4	VH4-31-9	0	
4	VH4-31-10	0	
4	VH4-31-11	0	
4	VH4-31-12	4	
4	VH4-31-13	7	
4	VH4-31-14	0	
4	VH4-31-15	0	
4	VH4-31-16	0	
4	VH4-31-17	0	
4	VH4-31-18	0	
4	VH4-31-19	0	
4	VH4-31-20	0	57 entries
5	VH5-12-1	32	
5	VH5-12-2	1	
5	VH5-12-3	0	
5	VH5-12-4	14	97 entries
6	VH6-12-1	4	74 entries

Table 4A: Analysis of V kappa subgroup 1

amino acid ¹	Framework I															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A									1				102		1	
B			1			1										
C														1		
D	54															
E	88	4													1	
F									1	6				1		
G																105
H																
I															4	
K																
L											96		1			
M																
N																
P										1		2			1	
Q						88					1					
R																
S							89			80		103		103		
T					88					18						
V											8		2		98	
W																
X																
Y																
-																
unknown																
not sequenced					17	16										
sum of seq ²					88	89				105	105	105	105	105	105	105
oomcaa ³					88	88				80	96	103	102	103	98	105
mcaa ⁴					T	Q				S	L	S	A	S	V	G
rel. oomcaa ⁵					100%	99%				91%	98%	97%	98%	98%	93%	100%
pos occup ⁶					1	2				3	2	3	3	3	5	1

Table 4A: Analysis of V kappa s¹

p 1

amino acid ¹	17	18	21	22	26	27	A	B	C	D
A				1						
B						1				
C										
D	101									
E	2					2				
F			2							
G					1					
H						1				
I			101	1						
K						1				
L										
M										
N					1					
P										
Q						100				
R										
S					102					
T				102	1					
V			2							
W										
X										
Y										
-							105	105	105	105
unknown (?)										
not sequenced										
sum of seq ²			105	10	5	105	105	105	105	105
oomcaa ³			101	10	2	100	105	105	105	105
mcaa ⁴			1	1	0	-	-	-	-	-
rel. oomcaa ⁵			96%	100%	0%	95%	100%	100%	100%	100%
pos occupied ⁶			3	2	4	5	1	1	1	1

Table 4A: Analysis of V kappa group 1

		CDRI											
amino acid ¹	E	E	30	31	32	33	34	35	36	37	38	39	40
A			1				2						
B										1	1		
C					1								
D			1	5	7					1			
E										2			
F			1	1					6				
G			7										
H			1		2					2			
I			1				1						
K												95	
L			2			1							
M													
N			16				0						
P													102
Q										98	103	2	
R			16									3	1
S			57	3									1
T												1	
V			1										
W								104					
X													
Y			1						98				
-													
unknown (?)												3	
not sequenced								1	1	1	1	1	1
sum of seq ²			105	1				104	104	104	104	104	104
oomcaa ³			57					104	98	98	103	95	102
mcaa ⁴			S					W	Y	Q	Q	K	P
rel. oomcaa ⁵			54%					100%	94%	94%	99%	91%	98%
pos occupied ⁶			12					1	2	5	2	4	3

Table 4A: Analysis of V kappa sub 1

amino acid ¹	Frame		CDR II									
	41	42	45	46	47	48	50	51	52	53	54	55
A							50	95				
B												
C												
D							21	1	1	1		
E			1				1		1			33
F									1			
G							9	2				
H												1
I					1	1				1		
K			86				16			2		5
L				8							101	
M												
N			10				2		1	25		
P							1					1
Q			1									62
R			3							1	1	2
S			1				1	1	99	41	2	
T			1				1	4	1	31		
V								1		1		
W												
X			1							1		
Y							1					
-												
unknown (%)												
not sequence			1				2	1	1	1	1	1
sum of seq ²			104	1			103	104	104	104	104	104
oomcaa ³			86				50	95	99	41	101	62
mcaa ⁴			K				A	A	S	S	L	Q
rel. oomcaa ⁵			83%				49%	91%	95%	39%	97%	60%
pos occupi ⁶			8				10	6	6	9	3	6

Table 4A: Analysis of V kappa subgroup 1

amino acid ¹	56	57	60	61	62	63	65	66	67	68	69	70
A	3							2	1	1	1	
B												
C												
D	1											67
E										1		30
F					103				3			
G	2						4	101		102		
H												3
I	3				1	3						
K	1			1								1
L						1						
M											1	
N												
P			2									
Q							1					
R				103		1	1	1			2	
S			103			98			100			
T										101		
V												1
W												
X								1		1		2
Y									1			1
unknown (?)												
not sequenced												
sum of seq ²			105	10	10	10		105	105	105	105	105
oomcaa ³			103	10	10	98		101	100	102	101	67
meta ⁴			S	R	F	S		G	S	G	T	D
rel. oomcaa ⁵			98%	100%	100%	98%		99%	99.5%	97%	96%	64%
pos occupie ⁶			2	1	1	1		4	4	4	4	7

Table 4A: Analysis of V kappa subgroup 1

amino acid	75	76	77	78	81	82	83	84	85
A		1			2			101	1
B	1				2				
C									
D		1			16	101			
E					83				
F							73		
G			4		1			2	
H									
I	99	5					17		
K									
L				103			1		
M									1
N			4						1
P									1
Q									
R		2	1						
S	1	80	94				1		
T	2	2	1						97
V		4					11		1
W									
X	1				1	2			
Y									
-									
unknown (.)									
not sequenced	1	1			2	2	2	2	3
sum of seq	1	104	10	10	103	103	103	103	102
conserved	2	99	8	1	83	101	73	101	97
motif		I	S	L	E	D	F	A	T
rel. conserved		95%			81%	98%	71%	98%	95%
pos conserved	3	3			5	2	5	2	6

Table 4A: Analysis of V kappa subgroup 1

amino acid	CDR III							CDR III						
	88	89	90	91	92	93	94	95	A	B	C	D	E	F
A			1	7	1			5	1					
B		2	3											
C	102													
D					22	1		1						
E								1	1					
F								3						
G								2	1	1				
H		4	6											
I								1						
K			7											
L		7						2						
M														
N														
P								82	6					
Q		90	86											
R														
S				2				10						
T														
V														
W														
X														
Y														
unknown								3	82	88	89	89	89	89
not sequenced	3	2	2					4	16	16	16	16	16	16
sum of amino acids	102	100	103	1				101	89	89	89	89	89	89
occurrence	102	90	86					82	82	88	89	89	89	89
no.	C	C	C					P	-	-	-	-	-	-
rel. occurrence	100%	97%	83%					81%	92%	99%	100%	100%	100%	100%
pos. charges	1	4	5					8	3	2	1	1	1	1

Table 4A: Analysis of V kappa subgroup 1

amino acid ¹	Framework IV														sum
	96	97	98	99	100	101	102	103	104	105	106	A	107	108	
A	1														627
B					1					1					19
C															209
D	1									15					459
E					2					65					258
F	6		86								2				451
G				87	29	87								2	894
H	2	1													40
I	5								1		72				606
K	1	1						77					79		480
L	18	1	1						22	4	2				793
M		1									5				77
N	1										1		2		232
P	6				7									1	620
Q	1				48					1					865
R	6							6					2	70	413
S	2	2													1636
T	2	82					87	3					2		1021
V	2							1	63		3				440
W	15														141
X															14
Y	16														564
-	4	1										85		1	1250
unknown (?)															7
not sequenced	16	16	18	18	18	18	18	18	19	19	20	20	20	31	589
sum of seq ²	89	89	87	87	87	87	87	87	86	86	85	85	85	74	
oomcaa ³	18	82	86	87	48	87	87	77	63	65	72	85	79	70	
mcaa ⁴	L	T	F	G	G	G	T	K	V	E	I	-	K	R	
rel. oomcaa ⁵	20%	92%	99%	100%	55%	100%	100%	89%	73%	76%	85%	100%	93%	95%	
pos occupied ⁶	17	7	2	1	5	1	1	4	3	5	6	1	4	4	

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Table 4B: Analysis of V kappa subgroup 2

Framework I																					
amino acid ¹	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
A																			22		
B																					
C																					
D	14																				
E	3																15				
F									1	1											
G																22					
H																					
I		8																			22
K																					
L		3		1					17	18					6						
M				15																	
N																					
P								18				18			15			22			
Q						18											7				
R																					
S							18			17										22	
T					17									21							
V		6	17	1									18								
W																					
X																					
Y																					
-																					
unknown (?)					1																
not sequenced	5	5	5	5	4	4	4	4	4	4	4	4	4	1	1						
sum of seq ²	17	17	17	17	18	18	18	18	18	18	18	18	18	21	21	22	22	22	22	22	22
oomcaa ³	14	8	17	15	17	18	18	18	17	17	18	18	18	21	15	22	15	22	22	22	22
mcaa ⁴	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I
rel. oomcaa ⁵	82%	47%	100%	88%	94%	100%	100%	100%	94%	94%	100%	100%	100%	100%	71%	100%	68%	100%	100%	100%	100%
pos occupied ⁶	2	3	1	3	1	1	1	1	2	2	1	1	1	1	2	1	2	1	1	1	1

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Table 4B: Analysis of V kappa subgroup 2

	CDRI																									
amino acid ¹	22	23	24	25	26	27	A	B	C	D	E	F	28	29	30	31	32	33	34	35	36					
A																										
B																										
C		22																								
D										1			9		1	1			11							
E																										
F															2										7	
G											1			22												
H										16							1		1							
I																										
K			1													1										
L						1		22	13									22								
M									1																	
N													10		7	12			9							
P																										
Q	1					21																				
R			21								2															
S	21			22	22	22					19		1													
T																8										
V									8																	
W										1															22	
X													1		1				1							
Y										4			1		11		21								15	
-											22															
unknown (?)																										
not sequenced																										
sum of seq ¹	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22
oomcaa ¹	21	22	21	22	22	21	22	22	13	16	19	22	10	22	11	12	21	22	11	22	15					
mcaa ¹	S	C	R	S	S	Q	S	L	L	H	S	-	N	G	Y	N	Y	L	D	W	Y					
rel. oomcaa ¹	95%	100%	95%	100%	100%	95%	100%	100%	59%	73%	86%	100%	45%	100%	50%	55%	95%	100%	50%	100%	68%					
pos occupied ¹	2	1	2	1	1	2	1	1	3	4	3	1	5	1	5	4	2	1	4	1	2					

Table 4B: Analysis of V kappa subgroup 2

	Framework II													CDR II												
amino acid ¹	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57					
A																			14							
B																										
C																										
D																			7							
E									1																	
F																										
G				22											12				1	22						
H																										
I										1	22															
K			15											5												
L	16									14	21			14	1											
M																										
N																	18									
P				22				21																		
Q	6	22				22			12					1												
R			7						8	7				1				22								
S						21									2	22	2			22						
T																	1									
V											1				6											
W																										
X																										
Y													21				1									
-																										
unknown (?)																										
not sequenced							1	1	1				1	1	1											
sum of seq ²	22	22	22	22	22	22	21	21	21	22	22	22	21	21	21	22	22	22	22	22	22					
oomcaa ³	16	22	15	22	22	22	21	21	12	14	21	22	21	14	12	22	18	22	14	22	22					
mcaa ⁴	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R	A	S	G					
rel. oomcaa ⁵	73%	100%	68%	100%	100%	100%	100%	100%	57%	64%	95%	100%	100%	67%	57%	100%	82%	100%	64%	100%	100%					
pos occupied ⁶	2	1	2	1	1	1	1	1	3	3	2	1	1	4	4	1	4	1	3	1	1					

Table 4B: Analysis of V kappa subgroup 2

	Framework III																					
amino acid ¹	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	
A																						
B																						
C																						
D			22				1				1		22									
E																						
F					21									22								
G							21		22		21											
H																						
I																	1	21				
K																	19					
L																21	1					
M																						
N																						
P		22																				
Q																						
R				20				1												20		
S				1		22		21		22									20	1		
T				1								22			21				1			
V	22				1																21	
W																						
X																						
Y																						
-																						
unknown (?)															1							
not sequenced																	1	1	1	1	1	
sum of seq ²	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	21	21	21	21	21	21	
oomcaa ³	22	22	22	20	21	22	21	21	22	22	21	22	22	22	21	21	19	21	20	20	21	
mcaa ⁴	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V	
rel. oomcaa ⁵	100%	100%	100%	91%	95%	100%	95%	95%	100%	100%	95%	100%	100%	100%	95%	100%	90%	100%	95%	95%	100%	
pos occupied ⁶	1	1	1	3	2	1	2	2	1	1	2	1	1	1	1	1	3	1	2	2	1	

Table 4B: Analysis of V kappa subgroup 2

amino acid ¹											CDR III										
	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	A	B	C	D
A		20											14			1					
B												1			1						
C										21											
D				1	21																
E	19		20																		
F																					
G	1					21							6			1		2			
H													1		7						
I							1									1					
K																					
L							1							12			2				
M										21											
N																					
P		1														2	16	1			
Q	1											20			13						
R														1							
S																3	2				
T														8		7					
V					21		19														
W																6					
X																					
Y								21	21												
-																		14	17	17	17
unknown (?)																					
not sequenced ²	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	5	5	5	5
sum of seq ³	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	20	17	17	17	17
oomcaa ³	19	20	20	21	21	21	19	21	21	21	21	20	14	12	13	7	16	14	17	17	17
mcaa ⁴	E	A	E	D	V	G	V	Y	Y	C	M	Q	A	L	Q	T	P	-	-	-	-
rel. oomcaa ⁵	90%	95%	95%	100%	100%	100%	90%	100%	100%	100%	100%	95%	67%	57%	62%	33%	80%	82%	100%	100%	100%
pos occupied ⁶	3	2	2	1	1	1	3	1	1	1	1	2	3	3	3	7	3	3	1	1	1

Table 4B: Analysis of V kappa subgroup 2

	Framework IV																	
amino acid ¹	E	F	96	97	98	99	100	101	102	103	104	105	106	A	107	108	sum	
A																	71	
B												1					3	
C																	43	
D																	112	
E												13					71	
F			1		17												72	
G					17	2	16					1					233	
H																	26	
I			3										14				94	
K										12					13		66	
L			2								11						219	
M																	37	
N																	56	
P			1														159	
Q			1				14										159	
R										4						12	126	
S																	325	
T				17					16								140	
V												5					146	
W			2														31	
X																	3	
Y			7														123	
-	17	17												13			134	
unknown (?)																	2	
not sequenced ⁶	5	5	5	5	5	5	6	6	6	6	6	7	8	9	9	10	211	
sum of seq ⁷	17	17	17	17	17	17	16	16	16	16	16	15	14	13	13	12		
oomcaa ¹	17	17	7	17	17	17	14	16	16	12	11	13	14	13	13	12		
mcaa ¹¹	-	-	Y	T	F	G	Q	G	T	K	L	E	I	-	K	R		
rel. oomcaa ⁵	100%	100%	41%	100%	100%	100%	88%	100%	100%	75%	69%	87%	100%	100%	100%	100%		
pos occupied ⁶	1	1	7	1	1	1	2	1	1	2	2	3	1	1	1	1		

Table 4C: Analysis of V kappa subgroup 3

Framework I																
amino acid ¹	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A		5					2		27						1	
B	1															
C												2				
D	2								14							
E	76		27													
F		1													1	
G	1								82						1	152
H										1						
I		75														
K	3															
L		4	1	104			1				150		129		1	
M	5			13												
N															5	
P								124							147	
Q						123										
R					1											
S							119		3	1		150	1	141		
T		2			117					147					5	1
V		1	89	1			1				1		22		1	
W																
X																
Y																
-																
unknown (?)																
not sequenced																
sum of seq ²	88	88	117	118	118	123	123	124	126	149	151	152	152	152	152	152
oomcaa ¹	76	75	89	104	117	123	119	124	82	147	150	150	129	141	147	152
mcaa ¹	E	I	V	L	T	Q	S	P	G	T	L	S	L	S	P	G
rel. oomcaa ³	86%	85%	76%	88%	99%	100%	97%	100%	65%	99%	99%	99%	85%	93%	97%	100%
pos occupied ⁴	6	6	3	3	2	1	4	1	4	3	2	2	3	4	6	1

Table 4C: Analysis of V kappa subgroup 3

	CDRI															
amino acid ¹	17	18	19	20	21	22	23	24	25	26	27	A	B	C	D	E
A			178	2					166	1						
B																
C							181			1						
D	6															
E	146	1									1					
F					7	1										
G	1	1							1	1		1				
H											17					
I		1		5	2											
K		1						5								
L					173						1	1				
M																
N												9				
P																
Q											159					
R		175						176		1	1	10				
S						180			7	175		87				
T		1		174					7	2		1				
V		1	4	1					1			1				
W								1								
X																
Y						1					1					
-												72	182	182	182	182
unknown (?)											1					
not sequenced																
sum of seq ²	153	181	182	182	182	182	181	182	182	181	181	182	182	182	182	182
oomcaa ³	146	175	178	174	173	180	181	176	166	175	159	87	182	182	182	182
mcaa ⁴	E	R	A	T	L	S	C	R	A	S	Q	S	-	-	-	-
rel. oomcaa ⁵	95%	97%	98%	96%	95%	99%	100%	97%	91%	97%	88%	48%	100%	100%	100%	100%
pos occupied ⁶	3	7	2	4	3	3	1	3	5	6	6	8	1	1	1	1

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[illegible]

Figure 4B: V lambda 2 (N2) gene sequence

Q S A L T Q P A S V S G S P G Q
 ~~~~~  
 sexAI  
 ~~~~~  
 CAGAGCGCAC TGACCCAGCC AGCTTCAGTG AGCGGCTCAC CAGGTCAGAG
 GTCTCGCGTG ACTGGGTCGG TCGAAGTCAC TCGCCGAGTG GTCCAGTCTC
 Eco57I
 ~~~~~  
 I T I S C T G T S S D V G G Y N  
 BSSI  
 ~~~~~  
 CATTACCATC TCGTGACGG GTACTAGCAG CGATGTGGC GGCTATAACT
 GTAATGGTAG AGCACATGCC CATGATCGTC GCTACACCCG CCGATATTGA
 ~~~~~  
 Y V S W Y Q Q H P G K A P K L M I  
 KpnI  
 ~~~~~  
 ATGTGAGCTG GTACCAGCAG CATCCCGGA AGCGCCGAA ACTGATGATT
 TACACTCGAC CATGGTCGTC GTAGGGCCCT TCCGCGGCTT TGACTACTAA
 ~~~~~  
 Y D V S N R P S G V S N R F S G S  
 Bsu36I  
 ~~~~~  
 TATGATGTGA GCAACCGTCC CTCAGGCGTG AGCAACCGTT TTAGCGGATC
 ATACTACACT CGTTGGCAGG GAGTCCGCAC TCGTTGGCAA AATCGCCTAG

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Figure 4A: V lambda 1 (Vλ1) gene sequence (continued)

GATAACAACC	AGCGTCCCTC	AGGCGTGCCG	GATCGTTTAA	GCGGATCCAA												
CTATTGTTGG	TCGCAGGGAG	TCCGCACGGC	CTAGCAAAAT	CGCCTAGGTT												
S	G	T	S	A	S	L	A	I	T	G	L	Q	S	E	D	
BbsI																
~~~~~																
AAGCGGCACC	AGCGCGAGCC	TTGCGATTAC	GGCCCTGCAA	AGCGAAGACG												
TTCGCCGTGG	TCGCGCTCGG	AACGCTAATG	CCCGGACGTT	TCGCTTCTGC												
E	A	D	Y	Y	C	Q	Q	H	Y	T	T	P	P	V	F	G
AAGCGGATTA	TTATTGCCAG	CAGCATTATA	CCACCCCGCC	TGTGTTTGGC												
TTCGCCCTAAT	AATAACGGTC	GTCGTAATAT	GGTGGGCGG	ACACAAACCG												
G	G	T	K	L	T	V	L	G								
HpaI									MscI							
~~~~~									~~~~~							
GGCGGCACGA	AGTTAACCGT	TCTTGGC														
CCGCCGTGCT	TCAATTGGCA	AGAACCG														

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Figure 4A: V lambda 1 (N1) gene sequence

Q S V L T Q P P S V S G A P G Q R
 ~~~~~  
 CAGAGCGTGC TGACCCAGCC GCCTTCAGTG AGTGGCGCAC CAGGTCAGCG  
 GTCTCGCACG ACTGGGTCGG CGGAAGTCAC TCACCGCGTG GTCCAGTCGC  
 ~~~~~  
 Eco57I
 ~~~~~  
 S S S S N I G S N Y  
 ~~~~~  
 V T I S C S G S S S N I G S N Y
 ~~~~~  
 BssSI  
 ~~~~~  
 TGTGACCATC TCGTGTAGCG GCAGCAGCAG CAACATTGGC AGCAACTATG
 AACTGGTAG AGCACATCGC CGTCGTCGTC GTTGTAAACCG TCGTTGATAC
 ~~~~~  
 V S W Y Q Q L P G T A P K L L I Y  
 ~~~~~  
 KpnI
 ~~~~~  
 TGAGCTGGTA CCAGCAGTTG CCCGGGACGG CGCCGAAACT GCTGATTAT  
 ACTCGACCAT GGTCTCAAC GGGCCCTGCC GCGGCTTTGA CGACTAAATA  
 ~~~~~  
 D N N Q R P S G V P D R F S G S K
 ~~~~~  
 Bsu36I  
 ~~~~~  
 BamHI
 ~~~~~

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Figure 3D: V kappa 4 (Vk4) gene sequence (continued)

|            |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|------------|------------|---|---|---|---|---|---|---|---|---|---|---|
| F          | S          | G          | S          | G          | S | G | T | D | F | T | L | T | I | S | S |
| BamHI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| TTTTAGCGC  | TCTGGATCCG | GCACTGATTT | TACCTGACC  | ATTTCGTCCC |   |   |   |   |   |   |   |   |   |   |   |
| AAAATCGCCG | AGACCTAGGC | CGTGACTAAA | ATGGGACTGG | TAAAGCAGGG |   |   |   |   |   |   |   |   |   |   |   |
| L          | Q          | A          | E          | D          | V | A | V | Y | C | Q | Q | H | Y | T | T |
| Eco57I     |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| BbsI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| TGCAAGCTGA | AGACGTGGCG | GTGTATTATT | GCCAGCAGCA | TTATACCACC |   |   |   |   |   |   |   |   |   |   |   |
| ACGTTCGACT | TCTGCACCCG | CACATAATAA | CGTCGTCGT  | AATATGGTGG |   |   |   |   |   |   |   |   |   |   |   |
| P          | P          | T          | F          | G          | Q | G | T | K | V | E | I | K | R | T |   |
| MscI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| CCGCCGACCT | TTGGCCAGGG | TACGAAAGTT | GAAATTAAAC | GTACG      |   |   |   |   |   |   |   |   |   |   |   |
| GGCGGCTGGA | AACCGGTCCC | ATGCTTTCAA | CTTTAATTG  | CATGC      |   |   |   |   |   |   |   |   |   |   |   |
| BsiWI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |

Figure 3D: V kappa 4 (Vx4) gene sequence

```

D I V M T Q S P D S L A V S L G E
EcoRV                               BanII
~~~~~
GATATCGTGA TGACCCAGAG CCCGGATAGC CTGGCGGTGA GCCTGGGCGA
CTATAGCACT ACTGGGTCTC GGGCCTATCG GACCGCCACT CGGACCCGCT

R A T I N C R S S Q S V L Y S S
PstI
~~~~~
ACGTGCGACC ATTAAGTGA GAAGCAGCCA GAGCGTGCTG TATAGCAGCA
TGCACGCTGG TAATTGACGT CTTCGTCGGT CTCGCACGAC ATATCGTCGT

N N K N Y L A W Y Q Q K P G Q P P
KpnI                               SexAI
~~~~~
ACAACAAAA CTATCTGGCG TGGTACCAGC AGAAACCAGG TCAGCCGCCC
TGTTGTTTAT GATAGACCGC ACCATGGTCC TCTTTGGTCC AGTCGGCGGC

K L L I Y W A S T R E S G V P D R
AseI SandI
~~~~~
AAACTATTAA TTTATTGGC ATCCACCCGT GAAAGCGGGG TCCCGGATCG
TTTGATAATT AAATAACCCG TAGGTGGGCA CTTTCGCCCC AGGCCCTAGC

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Figure 3C: V kappa 3 (Vκ3) gene sequence (continued)

CCGCGGCTCGT CGGCACGTTG ACCCCAGGGC CGCGCAAAT CGCCGAGACC

S G T D F T L T I S S L E P E D  
Eco57I  
~~~~~

BamHI
~~~~~  
ATCCGGCAG GATTTACCC TGACCATTAG CAGCCTGGAA CCTGAAGACT  
TAGGCCGTGC CTAAATGGG ACTGGTAATC GTCGGACCTT GGAATTCTGA

F A V Y Y C Q Q H Y T T P P T F G  
MscI  
~~~~~  
TTGCGGTGTA TTATTGCCAG CAGCATTATA CCACCCCGCC GACCTTTGGC
AACGCCACAT AATAACGGTC GTCGTAATAT GGTGGGGCGG CTGGAACCCG

Q G T K V E I K R T
MscI
~~~~~  
BsiWI  
~~~~~  
CAGGTACGA AAGTTGAAAT TAAACGTACG
GTCCCATGCT TTCAACTTA ATTGCATGC

Figure 3C: V kappa 3 (Vk3) gene sequence

```

D I V L T Q S P A T L S L S P G E
EcoRV
~~~~~
GATATCGTGC TGACCCAGAG CCCGGCGACC CTGAGCCTGT CTCCGGGGCGA
CTATAGCAGG ACTGGGTCTC GGGCCGCTGG GACTCGGACA GAGGCCCGCT

R A T L S C R A S Q S V S S S Y
PstI
~~~~~
ACGTGCGACC CTGAGCTGCA GAGCGAGCCA GAGCGTGAGC AGCAGCTATC
TGCACGCTGG GACTCGACGT CTCGCTCGGT CTCGCACTCG TCGTCGATAG

L A W Y Q Q K P G Q A P R L L I Y
KpnI SexAI AseI
~~~~~
TGGCGTGGTA CCAGCAGAAA CCAGGTCAAG CACCGCGTCT ATTAATTAT
ACCGCACCAT GGTCGTCTTT GTCCAGTTC GTGGCGCAGA TAATTAAATA

G A S S R A T G V P A R F S G S G
SandI BamHI
~~~~~
GGCGCGAGCA GCCGTGCAAC TGGGTCCTCCG GCGGTTTTA GCGGCTCTGG

```

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Figure 3B: V kappa 2 (Vκ2) gene sequence (continued)

S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
BamHI															
~~~~~															
TAGCGGCTCT	GGATCCGGCA	CCGATTTTAC	CCTGAAAATT	AGCCGTGTGG											
ATCGCCGAGA	CCTAGGCCGT	GGCTAAAATG	GGAATTTTAA	TCGGCACACC											
E	A	E	D	V	G	V	Y	Y	C	Q	Q	H	Y	T	P
Eco57I															
~~~~~															
BbsI															
~~~~~															
AAGCTGAAGA	CGTGGGCGTG	TATTATTGCC	AGCAGCATTA	TACCACCCCG											
TTCGACTTCT	GCACCCGCAC	ATAATAACGG	TCGTCGTAAT	ATGGTGGGGC											
P	T	F	G	Q	G	T	K	V	E	I	K	R	T		
MscI															
~~~~~															
CCGACCTTTG	GCCAGGGTAC	GAAAGTTGAA	ATTAAACGTA	CG											
GGCTGGAAC	CGGTCCCATG	CTTCAACTT	TAATTGCAT	GC											
BsiWI															
~~~~~															



Figure 3B: V kappa 2 (Vk2) gene sequence

```

D I V M T Q S P L S L P V T P G E
EcoRV
~~~~~
GATATCGTGA TGACCCAGAG CCCACTGAGC CTGCCAGTGA CTCCGGGCGA
CTATAGCACT ACTGGGTCTC GGTGACTCG GACGGTCACT GAGGCCCGCT

P A S I S C R S S Q S L L H S N
PstI
~~~~~
GCCTGCGAGC ATTAGCTGCA GAAGCAGCCA AAGCCTGCTG CATAGCAACG
CGGACGCTCG TAATCGACGT CTTCGTCTGGT TTCGGACGAC GTATCGTTGC

G Y N Y L D W Y L Q K P G Q S P Q
KpnI
~~~~~
GCTATAACTA TCTGGATTGG TACCTTCAA AACCAGGTCA AAGCCCGCAG
CGATATTGAT AGACCTAACC ATGGAAGTTT TTGGTCCAGT TTCGGGCGTC

L L I Y L G S N R A S G V P D R F
AseI
~~~~~
CTATTAATTT ATCTGGGCAG CAACCGTGCC AGTGGGGTCC CGGATCGTTT
GATAATTAAA TAGACCCGTC GTTGGCACGG TCACCCCGAG GCCTAGCAA
SandI
~~~~~

```

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Figure 3A: V kappa 1 (Vk1) gene sequence (continued)

CGGTCGTCGA ACGTTTCGCC CCAGGCGCAGG GCAAAATCGC CGAGACCTAG

G T D F T L T I S S L Q P E D F  
Eco57I  
~~~~~

BamHI

BbsI

CGGCACTGAT TTTACCCCTGA CCATTAGCAG CCTGCAACCT GAAGACTTTG  
GCCGTGACTA AAATGGGACT GGTAATCGTC GGACGTTGGA CTCTGAAAC

A T Y Y C Q Q H Y T T P P T F G Q  
MscI  
~~~~~

CGACCTATTA TTGCCAGCAG CATTATACCA CCCC GCCGAC CTTTGGCCAG  
GCTGGATAAT AACGGTCGTC GTAATATGGT GGGCGGGCTG GAAACCGGTC

G T K V E I K R T

BsiWI

GGTACGAAAG TTGAAATTAA ACGTACG  
CCATGCTTC AACTTTAATT TGCATGC  
~~~~~

Figure 3A: V kappa 1 (Nk1) gene sequence

```

.D I Q M T Q S P S S L S A S V G D
EcoRV BanII
~~~~~                               ~~~~~
GATATCCAGA TGACCCAGAG CCCGTCTAGC CTGAGCGCGA GCGTGGGTGA
CTATAGGTCT ACTGGGTCTC GGCAGATCG GACTCGCGCT CGCACCCACT

R V T I T C R A S Q G I S S Y L
PstI
~~~~~
TCGTGTGACC ATTACCTGCA GAGCGAGCCA GGCATTAGC AGCTATCTGG
AGCACACTGG TAATGGACGT CTCGCTCGGT CCCGTAATCG TCGATAGACC

A W Y Q Q K P G K A P K L L I Y A
KpnI SexAI
~~~~~                               ~~~~~
CGTGGTACCA GCAGAAACCA GGTAAGCAC CGAAACTATT AATTATGCA
GCACCATGGT CGTCTTTGGT CCATTTCGTG GCTTTGATAA TTAATACGT

A S S L Q S G V P S R F S G S G S
SandI                               BamHI
~~~~~                               ~~~~~
GCCAGCAGCT TGCAAAGCGG GGTCCCCTCC CGTTTAGCG GCTCTGGATC

```

Figure 2C: V heavy chain consensus sequences

| CDRII |    |    |    |    |    |    |    |    |    | framework 3 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |
|-------|----|----|----|----|----|----|----|----|----|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|
| 58    | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68          | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 |   |   |   |   |
| VH1A  | N  | Y  | A  | Q  | K  | F  | Q  | G  | R  | V           | T  | I  | T  | A  | D  | E  | S  | T  | S  | T  | A  | Y  | M  | E  | L  | S  | S  | L | R | S | E |
| VH1B  | N  | Y  | A  | Q  | K  | F  | Q  | G  | R  | V           | T  | M  | T  | R  | D  | T  | S  | I  | S  | T  | A  | Y  | M  | E  | L  | S  | S  | L | R | S | E |
| VH2   | Y  | Y  | S  | T  | S  | L  | K  | T  | R  | L           | T  | I  | S  | K  | D  | T  | S  | K  | N  | Q  | V  | V  | L  | T  | M  | T  | N  | M | D | P | V |
| VH3   | Y  | Y  | A  | D  | S  | V  | K  | G  | R  | F           | T  | I  | S  | R  | D  | N  | S  | K  | N  | T  | L  | Y  | L  | Q  | M  | N  | S  | L | R | A | E |
| VH4   | N  | Y  | N  | P  | S  | L  | K  | S  | R  | V           | T  | I  | S  | V  | D  | T  | S  | K  | N  | Q  | F  | S  | L  | K  | L  | S  | S  | V | T | A | A |
| VH5   | R  | Y  | S  | P  | S  | F  | Q  | G  | Q  | V           | T  | I  | S  | A  | D  | K  | S  | I  | S  | T  | A  | Y  | L  | Q  | W  | S  | S  | L | K | A | S |
| VH6   | D  | Y  | A  | V  | S  | V  | K  | S  | R  | I           | T  | I  | N  | P  | D  | T  | S  | K  | N  | Q  | F  | S  | L  | Q  | L  | N  | S  | V | T | P | E |

| framework 3 |    |    |    |    |    |    |    |    |    | CDRIII |    |    |    |     |   |   |   |     |     | framework 4 |     |     |     |     |     |     |     |     |     |     |   |   |
|-------------|----|----|----|----|----|----|----|----|----|--------|----|----|----|-----|---|---|---|-----|-----|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|---|
| 86          | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96     | 97 | 98 | 99 | 100 | A | B | C | 101 | 102 | 103         | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 |   |   |
| VH1A        | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH1B        | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH2         | D  | T  | A  | T  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH3         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH4         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH5         | D  | T  | A  | M  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |
| VH6         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G   | F | Y | A | M   | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S | S |

| framework 1 |   |   |
|-------------|---|---|
| 1           | Q | V |
| 2           | Q | V |
| 3           | Q | V |
| 4           | Q | V |
| 5           | Q | V |
| 6           | Q | V |
| 7           | Q | V |
| 8           | Q | V |
| 9           | Q | V |
| 10          | Q | V |
| 11          | Q | V |
| 12          | Q | V |
| 13          | Q | V |
| 14          | Q | V |
| 15          | Q | V |
| 16          | Q | V |
| 17          | Q | V |
| 18          | Q | V |
| 19          | Q | V |
| 20          | Q | V |
| 21          | Q | V |
| 22          | Q | V |
| 23          | Q | V |
| 24          | Q | V |
| 25          | Q | V |
| 26          | Q | V |
| 27          | Q | V |
| 28          | Q | V |
| 29          | Q | V |
| 30          | Q | V |

| framework 2 |   |   |
|-------------|---|---|
| 31          | S | A |
| 32          | S | A |
| 33          | S | A |
| 34          | S | A |
| 35          | S | A |
| 36          | S | A |
| 37          | S | A |
| 38          | S | A |
| 39          | S | A |
| 40          | S | A |
| 41          | S | A |
| 42          | S | A |
| 43          | S | A |
| 44          | S | A |
| 45          | S | A |
| 46          | S | A |
| 47          | S | A |
| 48          | S | A |
| 49          | S | A |
| 50          | S | A |
| 51          | S | A |
| 52          | S | A |
| 53          | S | A |
| 54          | S | A |
| 55          | S | A |
| 56          | S | A |
| 57          | S | A |

| framework 2 |   |   |
|-------------|---|---|
| 31          | S | A |
| 32          | S | A |
| 33          | S | A |
| 34          | S | A |
| 35          | S | A |
| 36          | S | A |
| 37          | S | A |
| 38          | S | A |
| 39          | S | A |
| 40          | S | A |
| 41          | S | A |
| 42          | S | A |
| 43          | S | A |
| 44          | S | A |
| 45          | S | A |
| 46          | S | A |
| 47          | S | A |
| 48          | S | A |
| 49          | S | A |
| 50          | S | A |
| 51          | S | A |
| 52          | S | A |
| 53          | S | A |
| 54          | S | A |
| 55          | S | A |
| 56          | S | A |
| 57          | S | A |

Figure 2B: VL lambda consensus sequences

| framework 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 58          | V | P | D | R | F | S | G | S | K | S | G | T | S | A | S | L | A | I | T | G | L | Q | S | E | D | E | A | D | Y | Y |
| 59          | V | S | N | R | F | S | G | S | K | S | G | N | T | A | S | L | T | I | S | G | L | Q | A | E | D | E | A | D | Y | Y |
| 60          | I | P | E | R | F | S | G | S | N | S | G | N | T | A | T | L | T | I | S | G | T | Q | A | E | D | E | A | D | Y | Y |
| 61          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 62          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 63          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 64          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 65          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 66          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 67          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 68          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 69          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 70          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 71          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 72          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 73          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 74          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 75          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 76          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 77          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 78          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 79          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 80          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 81          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 82          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 83          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 84          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 85          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 86          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 87          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| framework 4 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 88          | C | Q | Q | H | Y | T | T | P | P | V | F | G | G | G | T | K | L | T | V | L | G |
| 89          | C | Q | Q | H | Y | T | T | P | P | V | F | G | G | G | T | K | L | T | V | L | G |
| 90          | C | Q | Q | H | Y | T | T | P | P | V | F | G | G | G | T | K | L | T | V | L | G |
| 91          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 92          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 93          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 94          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 95          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 96          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 97          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 98          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 99          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 100         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 101         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 102         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 103         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 104         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 105         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 106         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 107         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

Figure 2B: VL lambda consensus sequences

| framework 1 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    | CDRI |    |    |    |    |    |    |    |    |    |    |    |   |   |
|-------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|------|----|----|----|----|----|----|----|----|----|----|----|---|---|
|             | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17   | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |   |   |
| VA1         | Q | S | V | L | T | Q | P | P | S | -  | V  | S  | G  | A  | P  | G  | Q    | R  | V  | T  | I  | S  | C  | S  | G  | S  | S  | N  | I |   |
| VA2         | Q | S | A | L | T | Q | P | A | S | -  | V  | S  | G  | S  | P  | G  | Q    | S  | I  | T  | I  | S  | C  | T  | G  | T  | S  | S  | D | V |
| VA3         | S | Y | E | L | T | Q | P | P | S | -  | V  | S  | V  | A  | P  | G  | Q    | T  | A  | R  | I  | S  | C  | S  | G  | D  | A  | -  | - | L |

| framework 2 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | CDR II |    |    |    |    |    |    |    |    |    |    |    |   |   |
|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--------|----|----|----|----|----|----|----|----|----|----|----|---|---|
| CDRI        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |        |    |    |    |    |    |    |    |    |    |    |    |   |   |
| 29          | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46     | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 |   |   |
| VA1         | G  | S  | N  | -  | Y  | V  | S  | W  | Y  | Q  | Q  | L  | P  | G  | T  | A  | P      | K  | L  | L  | I  | Y  | D  | N  | N  | Q  | R  | P  | S | G |
| VA2         | G  | G  | Y  | N  | Y  | V  | S  | W  | Y  | Q  | Q  | H  | P  | G  | K  | A  | P      | K  | L  | M  | I  | Y  | D  | V  | S  | N  | R  | P  | S | G |
| VA3         | G  | D  | K  | -  | Y  | A  | S  | W  | Y  | Q  | Q  | K  | P  | G  | Q  | A  | P      | V  | L  | V  | I  | Y  | D  | D  | S  | D  | R  | P  | S | G |

Figure 2A: VL kappa consensus sequences

| CDRIII |    | framework 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|--------|----|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vk1    | 55 | Q           | S | G | V | P | S | R | F | S | G | S | G | S | G | T | D | F | T | L | T |
| Vk2    | 56 | A           | S | G | V | P | D | R | F | S | G | S | G | S | G | T | D | F | T | L | K |
| Vk3    | 57 | A           | T | G | V | P | A | R | F | S | G | S | G | S | G | T | D | F | T | L | T |
| Vk4    | 58 | E           | S | G | V | P | D | R | F | S | G | S | G | S | G | T | D | F | T | L | T |
|        | 59 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 60 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 61 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 62 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 63 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 64 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 65 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 66 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 67 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 68 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 69 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 70 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 71 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 72 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 73 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 74 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 75 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 76 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 77 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 78 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 79 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 80 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 81 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 82 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 83 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|        | 84 |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| framework 3 |    | CDRIII |   | framework 4 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------|----|--------|---|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vk1         | 58 | T      | Y | Y           | C | Q | Q | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V |
| Vk2         | 59 | V      | Y | Y           | C | Q | Q | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V |
| Vk3         | 60 | V      | Y | Y           | C | Q | Q | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V |
| Vk4         | 61 | V      | Y | Y           | C | Q | Q | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V |
|             | 62 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 63 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 64 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 65 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 66 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 67 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 68 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 69 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 70 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 71 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 72 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 73 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 74 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 75 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 76 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 77 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 78 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 79 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 80 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 81 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 82 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 83 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|             | 84 |        |   |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |



Figure 2A: VL kappa consensus sequences

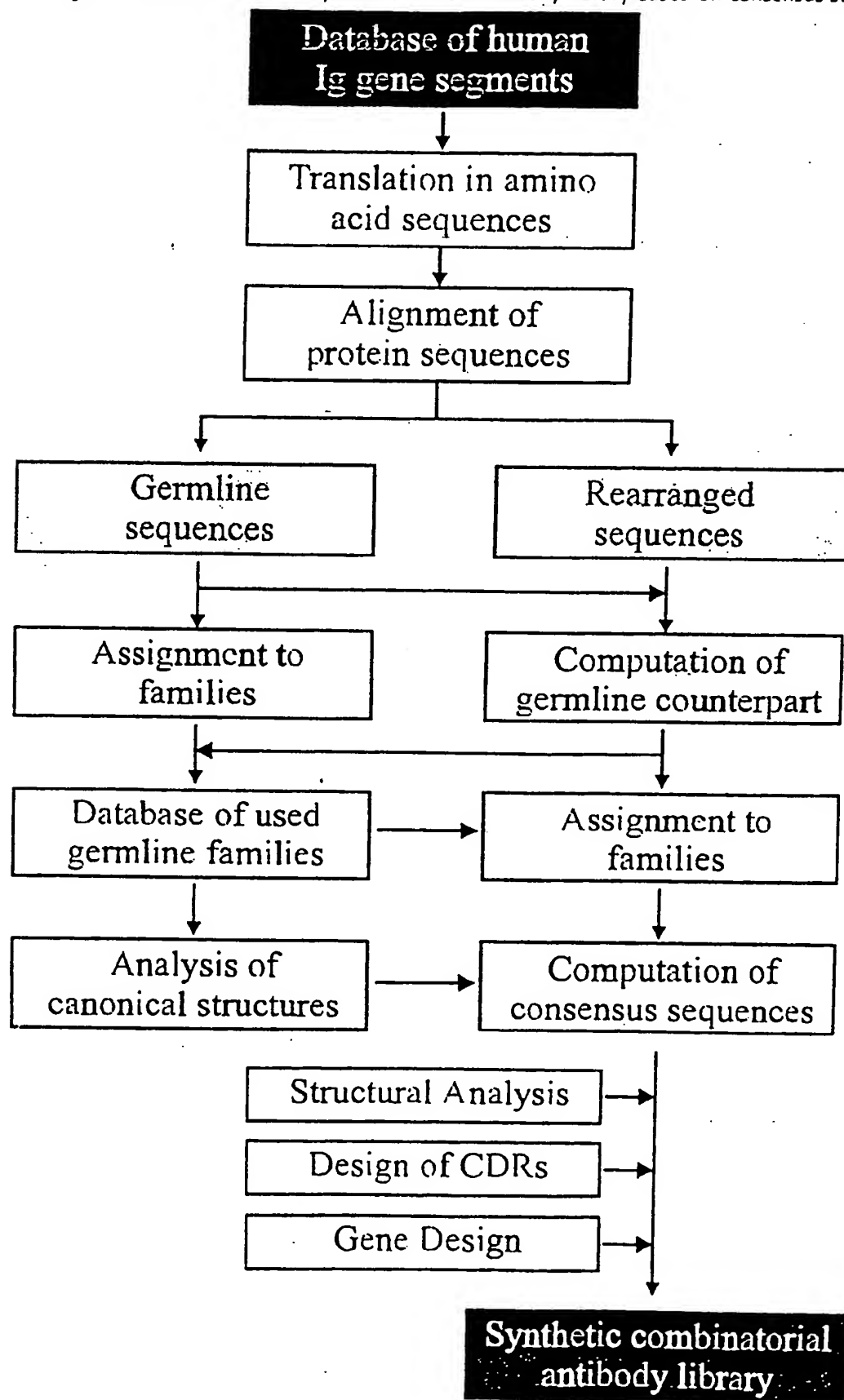
| framework 1 |                                                             | CDRI |       |
|-------------|-------------------------------------------------------------|------|-------|
|             |                                                             |      |       |
| Vκ1         | D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q - -   | 27   | A B C |
| Vκ2         | D I V M T Q S P L S L P V T P G E P A S I S C R S S Q S L L | 26   |       |
| Vκ3         | D I V L T Q S P A T L S L S P G E R A T L S C R A S Q S - - | 25   |       |
| Vκ4         | D I V M T Q S P D S L A V S L G E R A T I N C R S S Q S V L | 24   |       |
|             |                                                             | 23   |       |
|             |                                                             | 22   |       |
|             |                                                             | 21   |       |
|             |                                                             | 20   |       |
|             |                                                             | 19   |       |
|             |                                                             | 18   |       |
|             |                                                             | 17   |       |
|             |                                                             | 16   |       |
|             |                                                             | 15   |       |
|             |                                                             | 14   |       |
|             |                                                             | 13   |       |
|             |                                                             | 12   |       |
|             |                                                             | 11   |       |
|             |                                                             | 10   |       |
|             |                                                             | 9    |       |
|             |                                                             | 8    |       |
|             |                                                             | 7    |       |
|             |                                                             | 6    |       |
|             |                                                             | 5    |       |
|             |                                                             | 4    |       |
|             |                                                             | 3    |       |
|             |                                                             | 2    |       |
|             |                                                             | 1    |       |

| CDRI |                                                             | framework 2 |  | CDR II |  |
|------|-------------------------------------------------------------|-------------|--|--------|--|
|      |                                                             |             |  |        |  |
| Vκ1  | - - - G I S S Y L A W Y Q Q K P G K A P K L L I Y A S S L   | 54          |  | 51     |  |
| Vκ2  | H S - N G Y N Y L D W Y L Q K P G Q S P Q L L I Y L G S N R | 53          |  | 52     |  |
| Vκ3  | - - - V S S Y L A W Y Q Q K P G Q A P R L L I Y G A S S R   | 52          |  | 50     |  |
| Vκ4  | Y S S N N K N Y L A W Y Q Q K P G Q P P K L L I Y W A S T R | 51          |  | 49     |  |
|      |                                                             | 50          |  | 48     |  |
|      |                                                             | 49          |  | 47     |  |
|      |                                                             | 48          |  | 46     |  |
|      |                                                             | 47          |  | 45     |  |
|      |                                                             | 46          |  | 44     |  |
|      |                                                             | 45          |  | 43     |  |
|      |                                                             | 44          |  | 42     |  |
|      |                                                             | 43          |  | 41     |  |
|      |                                                             | 42          |  | 40     |  |
|      |                                                             | 41          |  | 39     |  |
|      |                                                             | 40          |  | 38     |  |
|      |                                                             | 39          |  | 37     |  |
|      |                                                             | 38          |  | 36     |  |
|      |                                                             | 37          |  | 35     |  |
|      |                                                             | 36          |  | 34     |  |
|      |                                                             | 35          |  | 33     |  |
|      |                                                             | 34          |  | 32     |  |
|      |                                                             | 33          |  | 31     |  |
|      |                                                             | 32          |  | 30     |  |
|      |                                                             | 31          |  | 29     |  |
|      |                                                             | 30          |  | 28     |  |
|      |                                                             | 29          |  | 27     |  |
|      |                                                             | 28          |  | 26     |  |
|      |                                                             | 27          |  | 25     |  |
|      |                                                             | 26          |  | 24     |  |
|      |                                                             | 25          |  | 23     |  |
|      |                                                             | 24          |  | 22     |  |
|      |                                                             | 23          |  | 21     |  |
|      |                                                             | 22          |  | 20     |  |
|      |                                                             | 21          |  | 19     |  |
|      |                                                             | 20          |  | 18     |  |
|      |                                                             | 19          |  | 17     |  |
|      |                                                             | 18          |  | 16     |  |
|      |                                                             | 17          |  | 15     |  |
|      |                                                             | 16          |  | 14     |  |
|      |                                                             | 15          |  | 13     |  |
|      |                                                             | 14          |  | 12     |  |
|      |                                                             | 13          |  | 11     |  |
|      |                                                             | 12          |  | 10     |  |
|      |                                                             | 11          |  | 9      |  |
|      |                                                             | 10          |  | 8      |  |
|      |                                                             | 9           |  | 7      |  |
|      |                                                             | 8           |  | 6      |  |
|      |                                                             | 7           |  | 5      |  |
|      |                                                             | 6           |  | 4      |  |
|      |                                                             | 5           |  | 3      |  |
|      |                                                             | 4           |  | 2      |  |
|      |                                                             | 3           |  | 1      |  |

SUBSTITUTE SHEET (RULE 26)

Figure 1: construction of a synthetic human antibody library based on consensus sequences



more second sub-sequences encoding structural sub-generate new vectors according to either of claims 50 or 51,

- (e) optionally, repeating steps (a) to (c).

54. A kit comprising two or more genes derived from gene sequences which:

- (a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and
- (b) carry cleavage sites, each of which:
  - (ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,
  - (bb) are unique within each gene sequence,
  - (bc) do not form compatible sites with respect to any single sub-sequence, and
  - (bd) are common to all homologous sub-sequences.

55. A kit comprising two or more genetic sub-sequences which encode structural sub-elements, which can be assembled to form genes, and which carry cleavage sites, each of which:

- (a) lie at or adjacent to the ends of said genetic sub-sequences,
- (b) do not form compatible sites with respect to any single sub-sequence, and
- (d) are common to all homologous sub-sequences.

51. The collection of vectors according to claim 50 comprising the additional feature that the vector does not comprise any cleavage site that is contained in the collection of genes according to any of claims 43 to 49.
52. A method for identifying one or more genes encoding one or more proteins having a desirable property, comprising the steps of:
- (a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins.
  - (b) screening said collection to isolate one or more proteins having a desired property,
  - (c) identifying the genes encoding the proteins isolated in step (b),
  - (d) optionally, excising from the genes encoding the proteins isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or more second sub-sequences encoding structural sub-elements, to generate new vectors according to either of claims 50 or 51,
  - (e) optionally, repeating steps (a) to (c).
53. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of:
- (a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins,
  - (b) screening said collection to isolate one or more antibody fragments which bind to said target,
  - (c) identifying the genes encoding the proteins isolated in step (b),
  - (d) optionally, excising from the genes encoding the antibody fragments isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or

- (b) carry cleavage sites, each of which:
  - (ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,
  - (bb) are unique within each gene sequence,
  - (bc) do not form compatible sites with respect to any single sub-sequence, and
  - (bd) are common to all homologous sub-sequences.
- 45. The collection of genes according to either of claims 43 or 44 in which each of said gene sequences has a nucleotide composition characteristic of a particular species.
- 46. The collection of genes according to claim 45 in which said species is human.
- 47. The collection of genes according to any of claims 43 to 46 in which one or more of said gene sequences encodes at least part of a member of the immunoglobulin superfamily, preferably of the immunoglobulin family.
- 48. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody heavy chains.
- 49. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody light chains.
- 50. A collection of vectors comprising a collection of gene sequences according to any of claims 43 to 49.

- (a) either
  - (aa) identifying two or more homologous gene sequences, or
  - (ab) analyzing at least three homologous genes, and deducing two or more consensus gene sequences therefrom,
- (b) optionally, modifying codons in said consensus gene sequences to remove unfavourable interactions between amino acids in the resulting proteins,
- (c) identifying sub-sequences which encode structural sub-elements in said consensus gene sequences
- (d) modifying one or more bases in regions adjacent to or between the ends of said sub-sequences to define one or more cleavage sites, each of which:
  - (da) are unique within each consensus gene sequence,
  - (db) do not form compatible sites with respect to any single sub-sequence,
  - (dc) are common to all homologous sub-sequences.

42. A method of preparing two or more genes encoding a collection of two or more proteins, comprising the steps of :

- (a) designing said genes according to claim 41, and
- (b) synthesizing said genes.

43. A collection of genes prepared according to the method of claim 42.

44. A collection of two or more genes derived from gene sequences which:

- (a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

34. A collection of host cells transformed with the collection of recombinant vectors according to claim 32.
35. A method of producing a (poly)peptide or a collection of (poly)peptides as defined in any of claims 1 to 28 comprising culturing the host cell according to claim 33 or the collection of host cells according to claim 34 under suitable conditions and isolating said (poly)peptide or said collection of (poly)peptides.
36. A (poly)peptide devisable by the method according to any one of claims 1 to 3, encoded by the nucleic acid sequence according to claim 29 or obtainable by the method according to any one of claims 4 to 28 or 35.
37. A collection of (poly)peptides devisable by the method according to any one of claims 1 to 3, encoded by the collection of nucleic acid sequences according to claim 30 or obtainable by the method according to any one of claims 4 to 28 or 35.
38. A vector suitable for use in the method according to any of claims 5 to 28 and 35 characterized in that said vector is essentially devoid of any cleavage site as defined in claim 1(e) and 2.
39. The vector according to claim 38 which is an expression vector.
40. A kit comprising at least one of:
- (a) a nucleic acid sequence according to claim 29;
  - (b) a collection of nucleic acid sequences according to claim 30;
  - (c) a recombinant vector according to claim 31;
  - (d) a collection of recombinant vectors according to claim 32;
  - (e) a (poly)peptide according to claim 36;
  - (f) a collection of (poly)peptides according to claim 37;
  - (g) a vector according to claim 38 or 39; and optionally,
  - (h) a suitable host cell for carrying out the method according to claim 35.
41. A method of designing two or more genes encoding a collection of two or more proteins, comprising the steps of:

24. The method according to claims 22 to 23, wherein said derivative is an scFv fragment comprising the combination of HuCAL VH3 and HuCAL Vλ2 consensus genes that comprises a random sub-sequence encoding the heavy chain CDR3 sub-element.
25. The method according to any one of claims 1 to 24, wherein at least part of said (poly)peptide sequences or (poly)peptides is connected to a sequence encoding at least one additional moiety or to at least one additional moiety, respectively.
26. The method according to claim 25, wherein said connection is formed via a contiguous nucleic acid sequence or amino acid sequence, respectively.
27. The method according to claims 25 to 26, wherein said additional moiety is a toxin, a cytokine, a reporter enzyme, a moiety being capable of binding a metal ion, a peptide, a tag suitable for detection and/or purification, or a homo- or hetero-association domain.
28. The method according to any one of claims 10 to 27, wherein the expression of said nucleic acid sequences results in the generation of a repertoire of biological activities and/or specificities, preferably in the generation of a repertoire based on a universal framework.
29. A nucleic acid sequence obtainable by the method according to any of claims 1 to 28.
30. A collection of nucleic acid sequences obtainable by the method according to any of claims 1 to 28.
31. A recombinant vector obtainable by the method according to any of claims 5 to 28.
32. A collection of recombinant vectors obtainable by the method according to any of claims 5 to 30.
33. A host cell transformed with the recombinant vector according to claim 31.



13. The method according to any one of claims 1 to 12, wherein said cleavage sites are sites cleaved by restriction enzymes.
14. The method according to any one of claims 1 to 13, wherein said structural sub-elements comprise between 1 and 150 amino acids.
15. The method according to claim 14, wherein said structural sub-elements comprise between 3 and 25 amino acids.
16. The method according to any one of claims 1 to 15, wherein said nucleic acid is DNA.
17. The method according to any one of claims 1 to 16, wherein said (poly)peptides have an amino acid pattern characteristic of a particular species.
18. The method according to claim 17, wherein said species is human.
19. The method according to any one of claims 1 to 18, wherein said (poly)peptides are at least part of members or derivatives of the immunoglobulin superfamily.
20. The method according to claim 19, wherein said members or derivatives of the immunoglobulin superfamily are members or derivatives of the immunoglobulin family.
21. The method according to claim 19 or 20, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3.
22. The method according to claim 20 or 21, wherein said (poly)peptides are or are derived from the HuCAL consensus genes:  
Vk1, Vk2, Vk3, Vk4, Vλ1, Vλ2, Vλ3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, Cκ, Cλ, CH1 or any combination of said HuCAL consensus genes.
23. The method according to any one of claims 20 to 22, wherein said derivative of said immunoglobulin family or said combination is an Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragment.

6. The method according to any one of claims 1 to 5, wherein said removal of unfavorable interactions results in enhanced expression of said (poly)peptides.
7. The method according to any one of claims 1 to 6, further comprising the steps of:
  - (f) cleaving at least two of said cleavage sites located in regions adjacent to or between the ends of said sub-sequences; and
  - (g) exchanging said sub-sequences by different sequences; and
  - (h) optionally, repeating steps (f) and (g) one or more times.
8. The method according to claim 7, wherein said different sequences are selected from the group of different sub-sequences encoding the same or different sub-elements derived from the same or different (poly)peptides.
9. The method according to claims 7 or 8, wherein said different sequences are selected from the group of:
  - (i) genomic sequences or sequences derived from genomic sequences;
  - (ii) rearranged genomic sequences or sequences derived from rearranged genomic sequences; and
  - (iii) random sequences.
10. The method according to any one of claims 1 to 9 further comprising the expression of said nucleic acid coding sequences.
11. The method according to any one of claims 1 to 10 further comprising the steps of:
  - (i) screening, after expression, the resultant (poly)peptides for a desired property;
  - (k) optionally, repeating steps (f) to (i) one or more times with nucleic acid sequences encoding one or more (poly)peptides obtained in step (i).
12. The method according to claim 11, wherein said desired property is selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

**Claims**

1. A method of setting up one or more nucleic acid sequences encoding one or more (poly)peptide sequences suitable for the creation of libraries of (poly)peptides said (poly)peptide sequences comprising amino acid consensus sequences, said method comprising the following steps:
  - (a) deducing from a collection of at least three homologous proteins one or more (poly)peptide sequences comprising at least one amino acid consensus sequence;
  - (b) optionally, identifying amino acids in said (poly)peptide sequences to be modified so as to remove unfavorable interactions between amino acids within or between said or other (poly)peptide sequences;
  - (c) identifying at least one structural sub-element within each of said (poly)peptide sequences;
  - (d) backtranslating each of said (poly)peptide sequences into a corresponding coding nucleic acid sequence;
  - (e) setting up cleavage sites in regions adjacent to or between the ends of sub-sequences encoding said sub-elements, each of said cleavage sites:
    - (ea) being unique within each of said coding nucleic acid sequences;
    - (eb) being common to the corresponding sub-sequences of any said coding nucleic acids.
2. A method of setting up two or more sets of one or more nucleic acid sequences comprising executing the steps described in claim 1 for each of said sets with the additional provision that said cleavage sites are unique between said sets.
3. The method of claim 2 in which at least two of said sets are deduced from the same collection of at least three homologous proteins.
4. The method according to any one of claims 1 to 3, wherein said setting up further comprises the synthesis of said nucleic acid coding sequences.
5. The method according to any one of claims 1 to 4, further comprising the cloning of said nucleic acid coding sequences into a vector.

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## Appendix to Tables 1A-C

A. *References of rearranged sequences**References of rearranged human kappa sequences used for alignment*

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Table 6G: Analysis of V heavy chain subgroup 6

| amino acid <sup>1</sup>   | Framework IV |      |     |     |      |     |     |     |      |      |     |     | sum  |
|---------------------------|--------------|------|-----|-----|------|-----|-----|-----|------|------|-----|-----|------|
|                           | 102          | 103  | 104 | 105 | 106  | 107 | 108 | 109 | 110  | 111  | 112 | 113 |      |
| A                         |              |      |     |     |      |     | 2   |     |      |      |     |     | 494  |
| B                         |              |      |     |     |      |     |     |     |      |      |     |     |      |
| C                         |              |      |     |     |      |     |     |     |      |      |     |     | 147  |
| D                         |              |      |     |     |      |     |     | 1   |      |      |     |     | 403  |
| E                         |              |      |     |     |      |     |     |     |      |      |     |     | 186  |
| F                         | 2            |      |     |     |      |     |     |     |      |      | 2   |     | 150  |
| G                         |              |      | 49  |     | 50   |     |     |     |      |      |     |     | 571  |
| H                         | 2            |      |     |     |      |     |     |     |      |      |     |     | 18   |
| I                         | 9            |      |     |     |      | 3   |     | 1   |      |      |     |     | 304  |
| K                         |              |      |     | 1   |      |     | 1   |     |      |      |     |     | 293  |
| L                         | 5            |      |     |     |      |     | 26  |     |      |      |     |     | 632  |
| M                         |              |      |     |     |      |     | 8   |     |      |      |     |     | 31   |
| N                         |              |      |     |     |      |     |     |     |      |      |     |     | 436  |
| P                         | 4            |      |     | 6   |      |     |     |     |      |      |     | 1   | 387  |
| Q                         |              |      |     | 40  |      |     |     |     |      |      |     |     | 539  |
| R                         |              |      |     | 2   |      |     |     |     |      |      |     |     | 495  |
| S                         | 4            |      | 1   |     |      | 1   |     |     |      |      | 43  | 46  | 1271 |
| T                         |              |      |     |     |      | 45  | 4   |     | 45   |      |     |     | 640  |
| V                         | 21           |      |     |     |      |     | 2   | 46  |      | 48   |     |     | 647  |
| W                         |              | 65   |     |     |      |     | 5   |     |      |      |     |     | 398  |
| X                         |              |      |     |     |      |     |     |     |      |      |     |     |      |
| Y                         | 19           |      |     |     |      |     |     |     |      |      |     |     | 518  |
| Z                         |              |      |     |     |      |     |     |     |      |      |     |     |      |
| -                         | 2            |      |     |     |      |     |     |     |      |      |     |     | 585  |
| unknown (?)               |              |      |     |     |      |     |     |     |      |      |     |     | 13   |
| not sequenced             | 5            | 8    | 23  | 24  | 23   | 24  | 25  | 25  | 28   | 25   | 28  | 26  | 580  |
| sum of seq <sup>2</sup>   | 68           | 65   | 50  | 49  | 50   | 49  | 48  | 48  | 45   | 48   | 45  | 47  |      |
| oomcaa <sup>3</sup>       | 21           | 65   | 49  | 40  | 50   | 45  | 26  | 46  | 45   | 48   | 43  | 46  |      |
| mcaa <sup>4</sup>         | V            | W    | G   | Q   | G    | T   | L   | V   | T    | V    | S   | S   |      |
| rel. oomcaa <sup>5</sup>  | 31%          | 100% | 98% | 82% | 100% | 92% | 54% | 96% | 100% | 100% | 96% | 98% |      |
| pos occupied <sup>6</sup> | 9            | 1    | 2   | 4   | 1    | 3   | 7   | 3   | 1    | 1    | 2   | 2   |      |

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Table 6G: Analysis of V heavy chain subgroup 6

|                           |     | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|---------------------------|-----|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | 93  | 94      | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   | 101 |  |
| A                         | 69  |         | 11  | 1   | 3   | 12  | 4   | 3   | 2   | 5   |     | 8   |     |     |     |     |     | 10  | 1   |     |  |
| B                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| C                         |     |         |     |     | 1   |     | 1   |     |     | 1   |     | 1   | 1   |     |     |     |     |     |     |     |  |
| D                         |     |         | 19  | 4   | 3   | 7   | 4   | 3   | 1   | 6   | 1   | 1   | 1   |     |     |     |     |     |     | 62  |  |
| E                         |     |         | 10  | 4   | 2   | 1   | 2   | 2   | 1   | 2   |     |     |     |     |     |     | 1   |     |     |     |  |
| F                         | 1   |         | 1   | 1   | 1   |     | 1   | 2   | 3   |     | 2   |     |     | 1   |     |     |     |     | 38  | 4   |  |
| G                         | 1   |         | 16  | 4   | 15  | 15  | 11  | 8   | 6   | 2   | 5   | 1   | 8   | 6   | 1   |     |     | 17  |     |     |  |
| H                         |     |         |     | 1   |     | 1   |     |     | 1   | 1   | 1   | 1   |     |     |     | 1   | 1   | 1   |     |     |  |
| I                         |     |         |     | 1   | 2   |     | 2   |     | 5   | 1   |     |     |     |     |     |     |     |     |     |     |  |
| K                         |     | 1       | 1   | 1   | 1   | 1   | 1   | 1   |     |     |     | 1   |     |     |     |     |     |     |     |     |  |
| L                         |     |         | 1   | 8   | 4   | 2   | 3   | 2   | 1   |     |     |     |     | 1   | 5   |     |     |     | 8   |     |  |
| M                         |     |         |     | 1   |     |     |     | 1   |     |     | 5   |     |     |     |     |     |     |     | 11  |     |  |
| N                         |     |         | 1   | 3   | 1   | 2   | 1   | 1   | 1   | 3   |     | 2   |     | 1   |     | 1   | 3   |     |     |     |  |
| P                         |     |         |     | 10  | 4   |     | 5   | 3   |     | 5   | 1   |     | 1   |     |     |     |     |     |     |     |  |
| Q                         |     |         | 1   | 1   | 1   | 1   |     |     |     |     | 1   |     |     |     |     |     |     |     |     | 1   |  |
| R                         |     | 69      | 1   | 7   | 8   | 1   | 8   | 8   | 3   |     | 1   | 1   | 5   |     |     |     |     |     |     | 1   |  |
| S                         |     | 3       | 5   | 5   | 5   | 7   | 6   | 7   | 3   | 4   | 2   |     |     |     |     | 1   | 1   |     |     |     |  |
| T                         |     |         | 1   | 1   | 4   | 3   | 4   | 4   | 6   | 3   | 1   |     |     | 1   |     |     |     |     |     |     |  |
| V                         | 3   | 1       | 4   | 5   | 1   | 9   |     |     | 4   |     | 9   | 5   | 1   | 1   |     |     |     |     | 2   |     |  |
| W                         |     |         | 1   | 6   | 8   |     | 3   | 2   | 4   |     |     |     |     |     |     |     | 4   | 4   |     |     |  |
| X                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| Y                         |     |         |     | 6   | 4   | 2   | 2   | 2   | 6   | 6   | 2   | 4   | 2   | 1   | 8   | 8   | 12  | 12  |     |     |  |
| Z                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| -                         |     |         |     | 2   | 3   | 7   | 14  | 23  | 25  | 33  | 41  | 47  | 53  | 54  | 57  | 56  | 50  | 28  | 12  | 4   |  |
| unknown (?)               |     |         |     |     |     |     |     |     |     |     |     |     |     | 6   | 1   | 5   |     |     |     |     |  |
| not sequenced             |     |         |     | 1   | 2   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   |  |
| sum of seq <sup>2</sup>   | 74  | 74      | 73  | 72  | 71  | 71  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  |  |
| oomcaa <sup>3</sup>       | 69  | 69      | 19  | 10  | 15  | 15  | 14  | 23  | 25  | 33  | 41  | 47  | 53  | 54  | 57  | 56  | 50  | 28  | 38  | 62  |  |
| mcaa <sup>4</sup>         | A   | R       | D   | P   | G   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |  |
| rel. oomcaa <sup>5</sup>  | 93% | 93%     | 26% | 14% | 21% | 21% | 19% | 32% | 35% | 46% | 57% | 65% | 74% | 75% | 79% | 78% | 69% | 39% | 53% | 86% |  |
| pos occupied <sup>6</sup> | 4   | 4       | 14  | 20  | 19  | 15  | 17  | 16  | 16  | 13  | 13  | 11  | 8   | 8   | 4   | 5   | 7   | 6   | 6   | 5   |  |

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Table 6G: Analysis of V heavy chain subgroup 6

| Framework III             |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
|---------------------------|------|-----|-----|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | 76   | 77  | 78  | 79   | 80   | 81  | 82  | A   | B   | C   | 83  | 84  | 85  | 86  | 87   | 88   | 89  | 90  | 91  | 92  |  |
| A                         |      |     |     |      |      |     |     |     |     |     |     |     | 1   |     |      | 74   |     |     |     |     |  |
| B                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| C                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     | 73  |  |
| D                         |      |     |     |      |      |     |     | 3   |     |     |     |     |     | 73  |      |      |     |     |     |     |  |
| E                         |      |     |     |      |      |     |     |     |     |     |     |     | 73  |     |      |      |     |     |     |     |  |
| F                         |      |     | 71  |      |      |     |     |     | 1   |     |     |     |     |     |      |      |     |     | 3   |     |  |
| G                         |      |     |     |      |      |     |     |     |     |     |     |     |     | 1   |      |      |     |     |     |     |  |
| H                         |      |     |     |      |      | 2   |     | 1   |     |     |     |     |     |     |      |      |     |     |     |     |  |
| I                         |      |     | 1   |      |      |     |     |     |     |     |     |     |     |     |      |      | 2   |     |     |     |  |
| K                         |      |     |     |      |      |     |     | 4   |     |     |     |     |     |     |      |      |     |     |     |     |  |
| L                         |      | 1   |     |      | 74   |     | 72  |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| M                         |      |     |     |      |      |     | 1   |     |     | 1   |     |     |     |     |      |      | 2   |     |     |     |  |
| N                         | 74   |     |     |      |      |     |     | 63  |     |     |     |     |     |     |      |      |     |     | 1   |     |  |
| P                         |      |     |     |      |      |     |     |     |     |     |     | 70  |     |     |      |      |     |     |     |     |  |
| Q                         |      | 72  |     |      |      | 71  |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| R                         |      | 1   |     |      |      | 1   |     | 1   |     |     |     |     |     |     |      |      |     |     |     | 1   |  |
| S                         |      |     |     | 74   |      |     |     | 1   | 73  |     | 1   | 3   |     |     |      |      |     |     |     |     |  |
| T                         |      |     |     |      |      |     |     | 1   |     |     | 73  |     |     |     | 74   |      |     | 1   |     |     |  |
| V                         |      |     | 2   |      |      |     | 1   |     |     | 73  |     |     |     |     |      |      | 70  |     |     |     |  |
| W                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| X                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| Y                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     | 73  | 70  |     |  |
| Z                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| -                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| unknown (?)               |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |  |
| not sequenced             |      |     |     |      |      |     |     |     |     |     | 1   |     |     |     |      |      |     |     |     |     |  |
| sum of seq <sup>7</sup>   | 74   | 74  | 74  | 74   | 74   | 74  | 74  | 74  | 74  | 74  | 74  | 73  | 74  | 74  | 74   | 74   | 74  | 74  | 74  | 74  |  |
| oomcaa <sup>3</sup>       | 74   | 72  | 71  | 74   | 74   | 71  | 72  | 63  | 73  | 73  | 73  | 70  | 73  | 73  | 74   | 74   | 70  | 73  | 70  | 73  |  |
| mcaa <sup>4</sup>         | N    | Q   | F   | S    | L    | Q   | L   | N   | S   | V   | T   | P   | E   | D   | T    | A    | V   | Y   | Y   | C   |  |
| rel. oomcaa <sup>5</sup>  | 100% | 97% | 96% | 100% | 100% | 96% | 97% | 85% | 99% | 99% | 99% | 96% | 99% | 99% | 100% | 100% | 95% | 99% | 95% | 99% |  |
| pos occupied <sup>6</sup> | 1    | 3   | 3   | 1    | 1    | 3   | 3   | 7   | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 1    | 3   | 2   | 3   | 2   |  |

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Table 6G: Analysis of V heavy chain subgroup 6

|                           | CDR II |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72  | 73  | 74  | 75  |  |  |  |  |
| A                         |        |     |     |     | 73  | 1   |     |     |     |     |     |     | 2   |     |     | 6   |     | 1   |     |     |  |  |  |  |
| B                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| C                         |        |     |     | 1   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| D                         |        |     | 68  |     |     | 1   |     |     |     |     |     |     |     |     | 2   |     | 73  |     |     |     |  |  |  |  |
| E                         | 1      |     | 3   |     |     | 7   |     |     | 1   |     |     |     |     |     |     |     |     |     |     | 2   |  |  |  |  |
| F                         | 7      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| G                         |        |     | 1   |     |     |     | 1   |     |     | 8   |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| H                         | 1      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     |  |  |  |  |
| I                         |        |     |     |     |     | 1   |     |     |     |     |     | 65  | 2   | 71  |     |     |     | 1   |     |     |  |  |  |  |
| K                         |        | 1   |     |     |     |     |     |     | 67  |     |     |     |     |     | 1   |     |     |     |     | 70  |  |  |  |  |
| L                         | 1      |     |     |     |     | 5   |     | 2   |     |     |     | 4   |     |     |     |     |     | 1   |     |     |  |  |  |  |
| M                         |        |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     |     |     |     |     |     |  |  |  |  |
| N                         | 2      | 65  | 1   |     |     |     |     |     | 1   |     |     |     |     |     | 69  |     |     |     |     |     |  |  |  |  |
| P                         |        |     |     |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     | 66  |     |     |     |  |  |  |  |
| Q                         |        |     |     |     |     |     |     |     | 2   |     | 1   |     |     |     |     |     |     |     |     |     |  |  |  |  |
| R                         |        | 1   |     |     |     |     |     |     | 3   |     | 73  |     |     |     |     |     |     |     |     |     |  |  |  |  |
| S                         | 2      | 2   | 1   | 1   |     |     | 73  |     |     | 66  |     |     | 1   |     | 2   | 1   |     |     | 73  |     |  |  |  |  |
| T                         |        | 4   |     |     |     |     |     |     |     |     |     |     | 69  | 1   |     |     |     | 71  | 1   | 2   |  |  |  |  |
| V                         |        |     |     |     | 58  |     | 72  |     |     |     |     | 4   |     | 2   |     | 1   |     |     |     |     |  |  |  |  |
| W                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| X                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| Y                         | 60     | 1   |     | 72  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| Z                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| -                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| unknown (?)               |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| not sequenced             |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 74     | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  |  |  |  |  |
| oomcaa <sup>3</sup>       | 60     | 65  | 68  | 72  | 73  | 58  | 73  | 72  | 67  | 66  | 73  | 65  | 69  | 71  | 69  | 66  | 73  | 71  | 73  | 70  |  |  |  |  |
| mcaa <sup>4</sup>         | Y      | N   | D   | Y   | A   | V   | S   | V   | K   | S   | R   | I   | T   | I   | N   | P   | D   | T   | S   | K   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 81%    | 88% | 92% | 97% | 99% | 78% | 99% | 97% | 91% | 89% | 99% | 88% | 93% | 96% | 93% | 89% | 99% | 96% | 99% | 95% |  |  |  |  |
| pos occupied <sup>6</sup> | 7      | 6   | 5   | 3   | 2   | 7   | 2   | 2   | 5   | 2   | 2   | 4   | 4   | 3   | 4   | 4   | 2   | 4   | 2   | 3   |  |  |  |  |

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Table 6G: Analysis of V heavy chain subgroup 6

|                           | Framework II |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
|---------------------------|--------------|------|-----|-----|-----|------|------|------|------|------|------|-----|-----|-----|-----|-----|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40   | 41  | 42  | 43  | 44   | 45   | 46   | 47   | 48   | 49   | 50  | 51  | 52  | A   | B   | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              |      |     | 1   |     |      |      |      |      |      |      |     | 1   |     |     |     |      | 1   |     |     |  |  |  |  |
| B                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| C                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| D                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| E                         |              |      |     |     |     |      |      | 74   |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| F                         |              |      |     |     |     |      |      |      |      |      |      |     |     | 2   | 1   |     |      | 1   |     |     |  |  |  |  |
| G                         |              |      |     |     |     | 74   |      |      |      |      | 74   | 1   |     |     |     |     |      |     | 1   |     |  |  |  |  |
| H                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     | 1   |     |      |     |     |     |  |  |  |  |
| I                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| K                         | 1            |      |     |     | 1   |      |      |      |      |      |      |     |     |     |     | 1   |      |     | 66  |     |  |  |  |  |
| L                         | 1            |      |     |     |     | 74   |      |      |      | 74   |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| M                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| N                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     | 1   |     |  |  |  |  |
| P                         |              |      | 73  |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| Q                         | 72           |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| R                         |              |      |     |     | 73  |      |      |      |      |      | 73   |     |     |     |     | 72  |      |     | 1   | 1   |  |  |  |  |
| S                         |              | 74   | 1   | 73  |     |      |      |      |      |      |      |     |     |     |     | 1   |      | 72  |     |     |  |  |  |  |
| T                         |              |      |     |     |     |      |      |      |      |      |      | 73  |     |     |     |     |      |     | 5   |     |  |  |  |  |
| V                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| W                         |              |      |     |     |     |      |      | 74   |      |      |      |     |     |     |     |     |      |     |     | 73  |  |  |  |  |
| X                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| Y                         |              |      |     |     |     |      |      |      |      |      |      |     |     | 72  | 72  |     |      |     |     |     |  |  |  |  |
| Z                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| -                         |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      | 74  |     |     |  |  |  |  |
| unknown (?)               |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| not sequenced             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 74           | 74   | 74  | 74  | 74  | 74   | 74   | 74   | 74   | 74   | 74   | 74  | 74  | 74  | 74  | 74  | 74   | 74  | 74  | 74  |  |  |  |  |
| oomcaa <sup>3</sup>       | 72           | 74   | 73  | 73  | 73  | 74   | 74   | 74   | 74   | 74   | 74   | 73  | 73  | 72  | 72  | 72  | 74   | 72  | 66  | 73  |  |  |  |  |
| mcaa <sup>4</sup>         | Q            | S    | P   | S   | R   | G    | L    | E    | W    | L    | G    | R   | T   | Y   | Y   | R   | -    | S   | K   | W   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 97%          | 100% | 99% | 99% | 99% | 100% | 100% | 100% | 100% | 100% | 100% | 99% | 99% | 97% | 97% | 97% | 100% | 97% | 89% | 99% |  |  |  |  |
| pos occupied <sup>6</sup> | 3            | 1    | 2   | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 3   | 3   | 1    | 3   | 5   | 2   |  |  |  |  |

Table 6G: Analysis of V heavy chain subgroup 6

| amino acid <sup>1</sup>   |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     | CDRI |     |      |     |      |
|---------------------------|-----|-----|-----|-----|------|------|-----|------|------|-----|-----|-----|-----|-----|-----|------|-----|------|-----|------|
|                           | 21  | 22  | 23  | 24  | 25   | 26   | 27  | 28   | 29   | 30  | 31  | A   | B   | 32  | 33  | 34   | 35  | 36   | 37  | 38   |
| A                         | 1   |     | 67  |     |      |      |     |      |      |     |     |     |     | 66  | 67  |      |     |      |     |      |
| B                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| C                         |     | 68  |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| D                         |     |     |     |     |      |      | 68  |      |      |     | 1   |     |     |     |     |      | 1   |      |     |      |
| E                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| F                         |     |     |     |     |      |      |     |      |      | 2   |     |     |     | 1   | 1   |      |     |      |     | 1    |
| G                         |     |     | 1   |     |      | 69   |     |      |      |     |     |     |     | 3   | 1   | 2    |     |      |     |      |
| H                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      | 1   |      |     |      |
| I                         |     |     |     | 64  |      |      |     |      |      |     |     | 2   |     |     |     |      | 1   |      | 70  |      |
| K                         |     |     |     |     |      |      |     |      |      |     |     | 3   |     |     |     |      |     |      |     |      |
| L                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| M                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| N                         |     |     |     |     |      |      | 1   |      |      |     | 2   | 66  |     |     |     |      | 70  |      |     |      |
| P                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| Q                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| R                         |     |     |     |     |      |      |     |      |      |     | 2   | 1   |     |     |     |      |     |      |     | 74   |
| S                         | 1   |     |     | 1   | 69   |      |     | 69   |      | 68  | 66  |     | 67  |     | 3   |      | 1   |      |     |      |
| T                         | 67  |     |     |     |      |      |     |      |      |     | 2   | 1   | 4   |     | 1   |      |     |      |     |      |
| V                         |     |     | 1   | 4   |      |      |     |      | 70   |     |     |     |     | 6   |     |      |     |      |     | 2    |
| W                         |     | 1   |     |     |      |      |     |      |      |     |     |     |     |     |     | 74   |     | 74   |     |      |
| X                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| Y                         |     |     |     |     |      |      |     |      |      |     |     | 1   |     |     |     |      |     |      |     | 1    |
| Z                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| -                         |     |     |     |     |      |      |     |      |      |     |     |     |     |     |     |      |     |      |     |      |
| unknown (?)               |     |     |     |     |      |      |     |      |      |     | 1   |     |     |     |     |      |     |      |     |      |
| not sequenced             | 5   | 5   | 5   | 5   | 5    | 5    | 5   | 5    | 4    | 4   |     |     |     |     |     |      |     |      |     |      |
| sum of seq <sup>1</sup>   | 69  | 69  | 69  | 69  | 69   | 69   | 69  | 69   | 70   | 70  | 74  | 74  | 74  | 74  | 74  | 74   | 74  | 74   | 74  | 74   |
| oomcaa <sup>3</sup>       | 67  | 68  | 67  | 64  | 69   | 69   | 68  | 69   | 70   | 68  | 66  | 66  | 67  | 66  | 67  | 74   | 70  | 74   | 70  | 74   |
| mcaa <sup>4</sup>         | T   | C   | A   | I   | S    | G    | D   | S    | V    | S   | S   | N   | S   | A   | A   | W    | N   | W    | I   | R    |
| rel. oomcaa <sup>5</sup>  | 97% | 99% | 97% | 93% | 100% | 100% | 99% | 100% | 100% | 97% | 89% | 89% | 91% | 89% | 91% | 100% | 95% | 100% | 95% | 100% |
| pos occupied <sup>6</sup> | 3   | 2   | 3   | 3   | 1    | 1    | 2   | 1    | 1    | 2   | 5   | 6   | 3   | 4   | 5   | 1    | 5   | 1    | 4   | 1    |

Table 6G: Analysis of V heavy chain subgroup 6

| amino acid <sup>1</sup>   | Framework I |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
|---------------------------|-------------|------|------|------|-----|------|------|------|------|------|-----|------|-----|------|-----|------|------|-----|-----|------|
|                           | 1           | 2    | 3    | 4    | 5   | 6    | 7    | 8    | 9    | 10   | 11  | 12   | 13  | 14   | 15  | 16   | 17   | 18  | 19  | 20   |
| A                         |             |      |      |      |     |      |      |      |      |      |     | 1    |     |      |     |      |      |     |     |      |
| B                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| C                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| D                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| E                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| F                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| G                         |             |      |      |      |     |      |      | 52   |      | 67   |     |      |     |      |     |      |      |     |     |      |
| H                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| I                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| K                         |             |      |      |      |     |      |      |      |      |      |     |      | 68  |      |     |      |      |     |     |      |
| L                         |             |      |      | 52   |     |      |      |      |      |      | 68  | 1    |     |      |     |      |      | 67  | 1   | 68   |
| M                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| N                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| P                         |             |      |      |      |     |      |      |      | 68   |      |     |      |     | 67   |     |      |      |     | 1   |      |
| Q                         | 52          |      | 52   |      | 51  | 52   |      |      |      |      |     |      |     |      |     | 68   |      |     |     |      |
| R                         |             |      |      |      | 1   |      |      |      |      | 1    |     |      |     |      |     |      |      |     |     |      |
| S                         |             |      |      |      |     |      | 52   |      |      |      |     |      |     | 1    | 68  |      |      |     | 66  |      |
| T                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      | 68   |     |     |      |
| V                         |             | 52   |      |      |     |      |      |      |      |      |     | 66   |     |      |     |      |      | 1   |     |      |
| W                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| X                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| Y                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| Z                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| -                         |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| unknown (?)               |             |      |      |      |     |      |      |      |      |      |     |      |     |      |     |      |      |     |     |      |
| not sequenced             | 22          | 22   | 22   | 22   | 22  | 22   | 22   | 22   | 22   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6    | 6   | 6   | 6    |
| sum of seq <sup>7</sup>   | 52          | 52   | 52   | 52   | 52  | 52   | 52   | 52   | 52   | 68   | 68  | 68   | 68  | 68   | 68  | 68   | 68   | 68  | 68  | 68   |
| oomcaa <sup>3</sup>       | 52          | 52   | 52   | 52   | 51  | 52   | 52   | 52   | 52   | 68   | 67  | 68   | 66  | 68   | 67  | 68   | 68   | 67  | 66  | 68   |
| mcaa <sup>4</sup>         | Q           | V    | Q    | L    | Q   | Q    | S    | G    | P    | G    | L   | V    | K   | P    | S   | Q    | T    | L   | S   | L    |
| rel. oomcaa <sup>5</sup>  | 100%        | 100% | 100% | 100% | 98% | 100% | 100% | 100% | 100% | 100% | 99% | 100% | 97% | 100% | 99% | 100% | 100% | 99% | 97% | 100% |
| pos occupied <sup>6</sup> | 1           | 1    | 1    | 1    | 2   | 1    | 1    | 1    | 1    | 2    | 1   | 3    | 1   | 2    | 1   | 1    | 1    | 2   | 3   | 1    |

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Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | Framework IV |      |      |     |      |     |     |     |     |      |     |     | sum  |
|---------------------------|--------------|------|------|-----|------|-----|-----|-----|-----|------|-----|-----|------|
|                           | 102          | 103  | 104  | 105 | 106  | 107 | 108 | 109 | 110 | 111  | 112 | 113 |      |
| A                         |              |      |      |     |      |     |     |     |     |      |     | 1   | 611  |
| B                         |              |      |      |     |      |     |     |     |     |      |     |     |      |
| C                         |              |      |      |     |      |     |     |     |     |      |     |     | 205  |
| D                         | 1            |      |      |     |      |     |     |     |     |      |     |     | 458  |
| E                         |              |      |      | 1   |      |     |     |     |     |      |     |     | 404  |
| F                         | 2            |      |      |     |      |     |     |     |     |      |     |     | 256  |
| G                         |              |      | 41   |     | 41   |     |     |     |     |      |     |     | 1065 |
| H                         |              |      |      |     |      |     |     |     |     |      |     |     | 44   |
| I                         | 9            |      |      |     |      |     |     |     | 2   |      |     |     | 588  |
| K                         |              |      |      | 3   |      |     |     |     |     |      |     |     | 650  |
| L                         | 2            |      |      |     |      |     | 25  | 1   |     |      |     |     | 549  |
| M                         |              |      |      |     |      |     | 8   |     |     |      |     |     | 303  |
| N                         |              |      |      |     |      |     |     |     |     |      |     |     | 64   |
| P                         | 2            |      |      |     |      | 1   |     |     |     |      | 1   |     | 414  |
| Q                         |              |      |      | 34  |      |     |     |     |     |      |     |     | 612  |
| R                         |              |      |      | 3   |      |     |     |     |     |      |     |     | 351  |
| S                         | 2            |      |      |     |      |     |     |     |     |      | 40  | 39  | 1545 |
| T                         | 1            |      |      |     |      | 40  | 8   |     | 39  |      |     |     | 604  |
| V                         | 11           |      |      |     |      |     |     | 40  |     | 41   |     |     | 594  |
| W                         |              | 43   |      |     |      |     |     |     |     |      |     |     | 432  |
| X                         |              |      |      |     |      |     |     |     |     |      |     |     |      |
| Y                         | 13           |      |      |     |      |     |     |     |     |      |     |     | 738  |
| Z                         |              |      |      |     |      |     |     |     |     |      |     |     |      |
| -                         | 2            |      |      |     |      |     |     |     |     |      |     |     | 635  |
| unknown (?)               |              |      |      |     |      |     |     |     |     |      |     |     | 4    |
| not sequenced             | 52           | 54   | 56   | 56  | 56   | 56  | 56  | 56  | 56  | 56   | 56  | 57  | 1678 |
| sum of seq <sup>2</sup>   | 45           | 43   | 41   | 41  | 41   | 41  | 41  | 41  | 41  | 41   | 41  | 40  |      |
| oomcaa <sup>3</sup>       | 13           | 43   | 41   | 34  | 41   | 40  | 25  | 40  | 39  | 41   | 40  | 39  |      |
| mcaa <sup>4</sup>         | Y            | W    | G    | Q   | G    | T   | L   | V   | T   | V    | S   | S   |      |
| rel. oomcaa <sup>5</sup>  | 29%          | 100% | 100% | 83% | 100% | 98% | 61% | 98% | 95% | 100% | 98% | 98% |      |
| pos occupied <sup>6</sup> | 10           | 1    | 1    | 4   | 1    | 2   | 3   | 2   | 2   | 1    | 2   | 2   |      |

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Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |
| A                         | 92      |     | 1   | 1   | 2   |     | 3   | 4   | 3   | 2   |     | 1   |     |     | 1   |     |     | 4   | 2   |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |         |     |     |     |     | 1   | 1   | 1   |     |     | 2   |     | 1   |     |     |     |     |     |     |
| D                         |         |     |     | 3   | 3   | 3   | 3   | 1   | 2   | 1   | 1   | 2   |     | 2   | 1   | 1   | 2   |     | 37  |
| E                         |         |     | 1   | 1   | 1   | 2   |     |     | 1   | 1   |     |     |     | 1   |     |     | 1   |     |     |
| F                         |         |     |     |     | 1   |     | 3   |     |     | 3   | 2   |     | 1   |     |     |     |     |     | 26  |
| G                         |         |     | 1   | 9   | 11  | 12  | 12  | 5   | 2   | 4   | 3   | 10  | 2   | 1   |     |     |     | 5   |     |
| H                         |         |     | 10  | 1   |     | 2   |     |     | 1   | 1   |     | 1   |     |     |     |     |     |     |     |
| I                         |         |     |     | 3   |     | 2   | 2   | 1   | 1   | 4   | 1   | 1   |     | 1   | 1   |     |     |     |     |
| K                         |         | 1   | 1   | 1   |     | 1   | 3   | 1   |     |     |     |     |     |     |     | 2   |     |     |     |
| L                         |         |     | 11  | 2   | 3   | 1   | 1   | 2   | 5   |     | 1   |     | 1   |     | 1   |     |     |     |     |
| M                         |         |     |     |     | 2   | 1   | 1   |     | 1   | 1   | 1   | 1   |     |     |     |     |     | 10  |     |
| N                         |         |     |     | 1   |     | 2   |     | 1   | 1   | 2   |     |     | 1   |     |     |     |     | 2   |     |
| P                         |         |     | 5   | 1   | 4   | 3   | 1   | 2   |     |     |     | 1   | 1   | 1   | 1   |     |     |     |     |
| Q                         |         | 1   | 3   | 2   |     | 1   | 1   | 4   | 2   | 1   | 2   |     |     |     |     |     |     |     | 3   |
| R                         |         | 92  | 7   | 9   | 2   | 2   |     | 2   | 1   |     | 2   |     |     |     |     |     |     |     |     |
| S                         |         | 1   | 1   | 3   | 2   | 6   | 4   | 4   | 5   | 3   | 5   | 3   | 2   | 2   |     |     | 1   |     | 1   |
| T                         | 1       |     | 1   | 3   | 2   | 1   | 2   | 6   | 3   | 3   | 6   | 1   |     | 1   |     |     |     |     |     |
| V                         | 2       |     | 2   | 4   | 4   |     | 1   |     | 1   | 2   |     |     | 1   |     |     |     |     |     |     |
| W                         |         |     | 1   |     | 2   | 1   |     |     |     |     | 1   |     | 2   |     | 1   |     | 1   | 1   |     |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |         |     |     | 1   | 6   | 3   | 6   | 9   | 8   | 7   | 2   | 1   | 2   | 6   | 8   | 9   | 9   | 10  | 1   |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |         |     |     |     |     | 1   | 1   | 2   | 8   | 10  | 16  | 23  | 30  | 30  | 31  | 32  | 30  | 22  | 7   |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     | 1   | 1   | 1   |     |
| not sequenced             | 2       | 2   | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  |
| sum of seq <sup>7</sup>   | 95      | 95  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 44  | 45  |
| oomcaa <sup>1</sup>       | 92      | 92  | 11  | 9   | 11  | 12  | 12  | 9   | 8   | 10  | 16  | 23  | 30  | 30  | 31  | 32  | 30  | 22  | 26  |
| mcaa <sup>1</sup>         | A       | R   | L   | G   | G   | G   | G   | Y   | Y   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |
| rel. oomcaa <sup>5</sup>  | 97%     | 97% | 24% | 20% | 24% | 27% | 27% | 20% | 18% | 22% | 36% | 51% | 67% | 67% | 69% | 71% | 67% | 49% | 59% |
| pos occupied <sup>6</sup> | 3       | 4   | 13  | 16  | 14  | 18  | 16  | 15  | 16  | 15  | 14  | 11  | 11  | 9   | 8   | 4   | 6   | 6   | 4   |

Table 6F: Analysis of V heavy chain subgroup 5

| Framework III             |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|
| amino acid <sup>1</sup>   | 76  | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    | 83  | 84  | 85  | 86  | 87  | 88  | 89  | 90  | 91  | 92   |  |
| A                         |     | 1   | 91  |     |     |     |     |     |     |      | 1   | 96  |     |     |     | 93  |     |     |     |      |  |
| B                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| C                         |     |     |     |     |     |     | 1   |     |     |      |     |     |     |     |     |     |     |     |     | 95   |  |
| D                         |     |     |     | 1   |     |     |     |     |     |      |     |     |     | 96  |     |     |     |     |     |      |  |
| E                         |     |     |     |     |     | 1   |     |     |     |      | 1   |     |     |     |     |     |     |     |     |      |  |
| F                         |     |     |     | 1   |     |     |     |     |     |      |     |     |     |     |     |     |     | 2   | 6   |      |  |
| G                         |     |     |     |     |     |     |     | 3   | 1   |      |     |     |     |     |     | 4   |     |     |     |      |  |
| H                         |     |     |     |     |     | 3   |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| I                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     | 2   |     | 9   |     |     |      |  |
| K                         |     |     |     |     |     |     |     |     |     |      | 91  |     |     |     |     |     | 1   |     |     |      |  |
| L                         |     |     |     |     | 96  |     |     |     |     | 97   |     |     |     |     |     |     | 2   |     |     |      |  |
| M                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 84  |     |     |      |  |
| N                         | 7   |     |     |     |     |     |     | 2   | 2   |      |     |     |     |     | 2   |     |     |     |     |      |  |
| P                         |     |     | 1   |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| Q                         |     |     |     |     |     | 93  |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| R                         | 1   |     |     |     |     |     | 1   | 1   | 3   |      | 3   |     |     |     |     |     |     |     |     |      |  |
| S                         | 87  | 2   | 1   | 1   |     |     |     | 90  | 91  |      |     |     | 96  |     | 5   |     |     |     |     |      |  |
| T                         | 2   | 94  | 2   |     |     |     |     | 1   |     |      | 1   | 1   | 1   |     | 88  |     | 1   |     |     |      |  |
| V                         |     |     | 2   |     | 1   |     |     |     |     |      |     |     |     | 1   |     |     |     |     |     |      |  |
| W                         |     |     |     |     |     |     | 95  |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| X                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| Y                         |     |     |     | 94  |     |     |     |     |     |      |     |     |     |     |     |     |     | 94  | 89  |      |  |
| Z                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| -                         |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| unknown (?)               |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |  |
| not sequenced             |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     | 1   | 2   | 2    |  |
| sum of seq <sup>2</sup>   | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 96  | 95  | 95   |  |
| oomcaa <sup>3</sup>       | 87  | 94  | 91  | 94  | 96  | 93  | 95  | 90  | 91  | 97   | 91  | 96  | 96  | 96  | 88  | 93  | 84  | 94  | 89  | 95   |  |
| mcaa <sup>4</sup>         | S   | T   | A   | Y   | L   | Q   | W   | S   | S   | L    | K   | A   | S   | D   | T   | A   | M   | Y   | Y   | C    |  |
| rel. oomcaa <sup>5</sup>  | 90% | 97% | 94% | 97% | 99% | 96% | 98% | 93% | 94% | 100% | 94% | 99% | 99% | 99% | 91% | 96% | 87% | 98% | 94% | 100% |  |
| pos occupied <sup>6</sup> | 4   | 3   | 5   | 4   | 2   | 3   | 3   | 5   | 4   | 1    | 5   | 2   | 2   | 2   | 4   | 2   | 5   | 2   | 2   | 1    |  |

Table 6F: Analysis of V heavy chain subgroup 5

|                           | CDR II |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|----|----|----|----|----|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72   | 73  | 74  | 75  |    |    |    |    |    |
| A                         |        | 6   |     |     |     |     | 1   |     |     |     |     |     |     |     |     | 88  |      |     |     |     |    |    |    |    |    |
| B                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| C                         |        |     |     |     | 1   |     |     |     |     | 1   |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| D                         | 77     |     |     |     |     |     |     |     |     | 2   |     |     |     |     |     |     | 97   |     |     |     |    |    |    |    |    |
| E                         | 3      |     |     |     |     |     |     |     | 2   |     |     |     |     |     |     |     |      |     | 2   |     |    |    |    |    |    |
| F                         |        |     |     | 2   |     |     |     | 91  |     |     |     | 1   |     | 3   |     |     |      |     |     |     |    |    |    |    |    |
| G                         | 1      |     |     |     |     |     |     |     |     | 94  |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| H                         |        |     |     |     |     |     |     |     |     |     | 15  |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| I                         |        | 4   | 1   |     |     |     |     | 1   |     |     |     | 3   | 88  |     |     |     |      |     |     | 91  |    |    |    |    |    |
| K                         |        |     | 2   |     |     |     |     |     |     |     |     |     |     |     |     |     |      | 93  |     |     |    |    |    |    |    |
| L                         |        |     |     |     |     | 1   |     | 4   |     |     |     |     |     |     | 2   |     |      |     |     |     |    |    |    |    |    |
| M                         |        |     |     |     |     |     |     |     |     |     |     |     |     | 3   |     |     |      |     |     | 1   |    |    |    |    |    |
| N                         | 2      |     | 14  | 2   |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| P                         |        |     |     |     |     | 95  | 1   |     | 1   |     |     |     |     |     |     |     |      |     | 1   |     |    |    |    |    |    |
| Q                         |        |     |     |     |     |     |     |     | 91  |     | 81  |     |     |     |     |     |      | 1   |     |     |    |    |    |    |    |
| R                         |        |     | 78  |     |     |     |     |     | 3   | 1   |     |     |     | 1   |     |     |      | 1   |     |     |    |    |    |    |    |
| S                         | 2      | 2   |     |     | 95  | 1   | 95  | 1   |     |     |     |     | 1   |     | 95  |     |      |     | 96  | 1   |    |    |    |    |    |
| T                         |        | 85  | 2   |     | 1   |     |     |     |     |     |     |     |     | 96  |     |     |      |     |     | 4   |    |    |    |    |    |
| V                         |        |     |     | 1   |     |     |     |     |     |     |     | 93  |     | 2   |     | 9   |      |     |     |     |    |    |    |    |    |
| W                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| X                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| Y                         | 12     |     |     | 92  |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| Z                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| -                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| unknown (?)               |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| not sequenced             |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |    |    |    |    |    |
| sum of seq <sup>2</sup>   | 97     | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97  | 97  | 97  | 97 | 97 | 97 | 97 | 97 |
| oomcaa <sup>3</sup>       | 77     | 85  | 78  | 92  | 95  | 95  | 95  | 91  | 91  | 94  | 81  | 93  | 96  | 88  | 95  | 88  | 97   | 93  | 96  | 91  |    |    |    |    |    |
| mcaa <sup>4</sup>         | D      | T   | R   | Y   | S   | P   | S   | F   | Q   | G   | Q   | V   | T   | I   | S   | A   | D    | K   | S   | I   |    |    |    |    |    |
| rel. oomcaa <sup>5</sup>  | 79%    | 88% | 80% | 95% | 98% | 98% | 98% | 94% | 94% | 97% | 84% | 96% | 99% | 91% | 98% | 91% | 100% | 96% | 99% | 94% |    |    |    |    |    |
| pos occupied <sup>6</sup> | 6      | 4   | 5   | 4   | 3   | 3   | 3   | 4   | 4   | 3   | 3   | 3   | 2   | 5   | 2   | 2   | 1    | 4   | 2   | 4   |    |    |    |    |    |

Table 6F: Analysis of V heavy chain subgroup 5

|                           | Framework II |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
|---------------------------|--------------|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41  | 42   | 43  | 44  | 45  | 46   | 47  | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              |     | 1   |      |     | 1   |     |      |     |     |     |     |     |     | 1   |      |      | 2   | 1   |     |  |  |  |  |
| B                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| C                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 1   |     |      |      | 1   |     |     |  |  |  |  |
| D                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 14  |     |      |      | 8   | 93  |     |  |  |  |  |
| E                         |              |     |     |      | 3   |     | 97  |      |     |     |     |     |     |     |     |      |      |     | 2   |     |  |  |  |  |
| F                         |              |     |     |      |     |     |     |      |     |     |     | 1   |     | 2   |     |      |      |     |     |     |  |  |  |  |
| G                         |              |     |     | 97   |     | 96  |     |      |     |     | 95  |     |     |     |     |      |      | 69  | 1   |     |  |  |  |  |
| H                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 3   | 1   |      |      |     |     |     |  |  |  |  |
| I                         |              |     |     |      |     |     |     |      |     | 1   |     | 75  | 92  |     |     |      |      |     |     |     |  |  |  |  |
| K                         |              | 1   |     |      | 94  |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| L                         |              |     |     |      |     | 94  |     |      |     | 2   |     | 2   | 1   |     |     |      |      |     |     |     |  |  |  |  |
| M                         |              | 92  |     |      |     |     |     |      |     | 89  |     |     | 1   |     |     |      |      |     |     |     |  |  |  |  |
| N                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| P                         |              |     | 96  |      |     |     | 2   |      |     |     |     |     |     | 1   | 93  |      |      |     |     | 1   |  |  |  |  |
| Q                         | 97           |     |     |      |     |     | 1   |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| R                         |              | 1   |     |      |     |     |     |      |     |     | 1   | 14  |     |     |     |      |      | 1   |     |     |  |  |  |  |
| S                         |              |     |     |      |     |     |     |      |     |     |     | 1   |     |     | 1   |      |      | 16  |     | 96  |  |  |  |  |
| T                         |              | 1   |     |      |     |     |     |      |     |     |     | 3   | 1   |     | 1   |      |      |     |     |     |  |  |  |  |
| V                         |              | 2   |     |      |     |     |     |      |     | 5   | 1   | 1   | 2   |     |     |      |      |     |     |     |  |  |  |  |
| W                         |              |     |     |      |     |     |     |      | 94  |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| X                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| Y                         |              |     |     |      |     |     |     |      | 3   |     |     |     |     | 76  |     |      |      |     |     |     |  |  |  |  |
| Z                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| -                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     | 97   | 97   |     |     |     |  |  |  |  |
| unknown (?)               |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| not sequenced             |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 97           | 97  | 97  | 97   | 97  | 97  | 97  | 97   | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97   | 97  | 97  | 97  |  |  |  |  |
| oomcaa <sup>1</sup>       | 97           | 92  | 96  | 97   | 94  | 96  | 94  | 97   | 94  | 89  | 95  | 75  | 92  | 76  | 93  | 97   | 97   | 69  | 93  | 96  |  |  |  |  |
| mcaa <sup>1</sup>         | Q            | M   | P   | G    | K   | G   | L   | E    | W   | M   | G   | I   | I   | Y   | P   | -    | -    | G   | D   | S   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 100%         | 95% | 99% | 100% | 97% | 99% | 97% | 100% | 97% | 92% | 98% | 77% | 95% | 78% | 96% | 100% | 100% | 71% | 96% | 99% |  |  |  |  |
| pos occupied <sup>6</sup> | 1            | 5   | 2   | 1    | 2   | 2   | 3   | 1    | 2   | 4   | 3   | 7   | 5   | 6   | 5   | 1    | 1    | 6   | 4   | 2   |  |  |  |  |

Table 6F: Analysis of V heavy chain subgroup 5

|                           |     |      |     |     |     |     |     |     |      |     | CDRI |      |      |     |     |     |     |      |     |     |
|---------------------------|-----|------|-----|-----|-----|-----|-----|-----|------|-----|------|------|------|-----|-----|-----|-----|------|-----|-----|
| amino acid <sup>1</sup>   | 21  | 22   | 23  | 24  | 25  | 26  | 27  | 28  | 29   | 30  | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38  |
| A                         |     |      |     | 3   | 2   |     |     |     |      | 4   |      |      |      |     |     |     | 8   |      | 1   |     |
| B                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     |     |     |     |      |     |     |
| C                         |     | 96   |     |     |     |     |     | 1   |      |     | 1    |      |      |     |     |     |     |      |     |     |
| D                         |     |      |     |     |     |     |     | 2   |      |     | 2    |      |      |     |     |     | 1   |      |     |     |
| E                         |     |      |     |     |     | 2   |     |     |      |     | 1    |      |      |     |     |     |     |      |     |     |
| F                         |     |      |     |     | 3   |     | 6   |     | 97   |     |      |      |      | 2   |     |     |     |      |     |     |
| G                         |     |      |     | 92  |     | 93  |     |     |      |     | 1    |      |      |     |     |     | 72  |      |     |     |
| H                         |     |      |     |     |     |     |     |     |      |     | 1    |      |      | 4   |     |     |     |      |     | 1   |
| I                         |     |      |     |     |     |     |     |     |      | 4   |      |      |      |     |     | 93  |     |      |     |     |
| K                         |     |      | 89  |     |     |     |     | 1   |      |     |      |      |      |     |     |     |     |      |     |     |
| L                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     | 1   |     |     |      | 2   |     |
| M                         |     |      | 1   |     |     |     |     |     |      |     |      |      |      |     |     | 1   |     |      | 1   |     |
| N                         |     |      | 1   |     |     |     |     | 2   |      | 4   | 14   |      |      | 2   |     |     |     |      |     |     |
| P                         |     |      |     |     | 1   |     |     |     |      |     |      |      |      |     |     |     |     |      |     | 1   |
| Q                         |     |      | 4   |     |     |     |     |     |      |     |      |      |      |     |     |     |     |      |     |     |
| R                         |     |      | 1   |     |     | 1   |     | 2   |      |     |      |      |      |     | 1   |     |     |      |     | 95  |
| S                         | 94  |      |     | 1   | 90  |     |     | 84  |      | 10  | 61   |      |      | 2   | 2   |     | 15  |      |     |     |
| T                         | 2   |      |     |     |     |     |     | 5   |      | 75  | 16   |      |      |     |     | 2   | 1   |      |     |     |
| V                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     |     | 1   |     |      | 93  |     |
| W                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     | 93  |     |     | 97   |     |     |
| X                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     |     |     |     |      |     |     |
| Y                         |     |      |     |     |     |     | 90  |     |      |     |      |      |      | 87  |     |     |     |      |     |     |
| Z                         |     |      |     |     |     |     |     |     |      |     |      |      |      |     |     |     |     |      |     |     |
| -                         |     |      |     |     |     |     |     |     |      |     | 97   | 97   |      |     |     |     |     |      |     |     |
| unknown (?)               |     |      |     |     |     |     |     |     |      |     |      |      |      |     |     |     |     |      |     |     |
| not sequenced             | 1   | 1    | 1   | 1   | 1   | 1   | 1   |     |      |     |      |      |      |     |     |     |     |      |     |     |
| sum of seq <sup>2</sup>   | 96  | 96   | 96  | 96  | 96  | 96  | 96  | 97  | 97   | 97  | 97   | 97   | 97   | 97  | 97  | 97  | 97  | 97   | 97  | 97  |
| oomcaa <sup>3</sup>       | 94  | 96   | 89  | 92  | 90  | 93  | 90  | 84  | 97   | 75  | 61   | 97   | 97   | 87  | 93  | 93  | 72  | 97   | 93  | 95  |
| mcaa <sup>4</sup>         | S   | C    | K   | G   | S   | G   | Y   | S   | F    | T   | S    | -    | -    | Y   | W   | I   | G   | W    | V   | R   |
| rel. oomcaa <sup>5</sup>  | 98% | 100% | 93% | 96% | 94% | 97% | 94% | 87% | 100% | 77% | 63%  | 100% | 100% | 90% | 96% | 96% | 74% | 100% | 96% | 98% |
| pos occupied <sup>6</sup> | 2   | 1    | 5   | 3   | 4   | 3   | 2   | 7   | 1    | 5   | 8    | 1    | 1    | 5   | 4   | 4   | 5   | 1    | 4   | 3   |

Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | Framework I |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
|---------------------------|-------------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|------|
|                           | 1           | 2   | 3    | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18   | 19  | 20   |
| A                         |             |     |      |     | 1   |     |     | 1   | 89  |     | 1   |     |     | 1   |     |     |     |      |     |      |
| B                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| C                         |             |     |      |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |      |     |      |
| D                         |             |     |      |     |     |     |     |     |     | 2   |     |     |     |     |     |     |     |      |     |      |
| E                         | 88          | 1   |      |     | 2   |     |     |     | 4   | 93  |     |     |     |     |     | 92  |     |      |     |      |
| F                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     | 1   |      |     |      |
| G                         | 1           |     |      |     |     |     |     | 92  |     |     |     |     |     |     | 94  |     |     |      |     |      |
| H                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| I                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     | 96   |
| K                         |             |     |      |     |     |     |     |     |     |     |     | 94  | 94  |     |     |     |     |      | 77  |      |
| L                         |             | 1   |      | 91  |     | 2   |     |     |     |     |     |     |     |     |     |     |     | 95   |     |      |
| M                         |             |     |      |     |     |     |     |     |     |     | 3   |     |     |     |     |     |     |      | 1   |      |
| N                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| P                         |             |     |      | 1   |     |     |     |     | 1   |     |     |     |     | 94  |     |     |     |      |     |      |
| Q                         | 3           |     | 92   |     | 1   | 90  |     |     |     |     |     |     |     |     |     |     | 3   |      | 1   |      |
| R                         |             |     |      |     |     | 1   |     |     |     |     |     | 1   | 1   |     | 1   |     |     |      | 17  |      |
| S                         |             |     |      |     |     |     | 92  |     |     |     |     |     |     |     |     |     | 94  |      |     |      |
| T                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| V                         |             | 90  |      |     | 89  |     |     |     | 1   | 91  |     |     |     |     |     |     |     |      |     |      |
| W                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| X                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| Y                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| Z                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| -                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| unknown (?)               |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| not sequenced             | 5           | 5   | 5    | 5   | 4   | 4   | 4   | 4   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2    | 1   | 1    |
| sum of seq <sup>1</sup>   | 92          | 92  | 92   | 92  | 93  | 93  | 93  | 93  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95   | 96  | 96   |
| oomcaa <sup>3</sup>       | 88          | 90  | 92   | 91  | 89  | 90  | 92  | 92  | 89  | 93  | 91  | 94  | 94  | 94  | 94  | 92  | 94  | 95   | 77  | 96   |
| mcaa <sup>4</sup>         | E           | V   | Q    | L   | V   | Q   | S   | G   | A   | E   | V   | K   | K   | P   | G   | E   | S   | L    | K   | I    |
| rel. oomcaa <sup>5</sup>  | 96%         | 98% | 100% | 99% | 96% | 97% | 99% | 99% | 94% | 98% | 96% | 99% | 99% | 99% | 99% | 97% | 99% | 100% | 80% | 100% |
| pos occupied <sup>6</sup> | 3           | 3   | 1    | 2   | 4   | 3   | 2   | 2   | 4   | 2   | 3   | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 4   | 1    |

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Table 6E: Analysis of V heavy chain subgroup 4

| Framework IV              |     |      |      |     |      |     |     |      |     |      |      |     |     | sum |
|---------------------------|-----|------|------|-----|------|-----|-----|------|-----|------|------|-----|-----|-----|
| amino acid <sup>1</sup>   | 102 | 103  | 104  | 105 | 106  | 107 | 108 | 109  | 110 | 111  | 112  | 113 |     |     |
| A                         |     |      |      |     |      | 1   |     |      | 1   |      |      |     | 332 |     |
| B                         |     |      |      |     |      |     |     |      |     |      |      |     |     |     |
| C                         |     |      |      |     |      |     |     |      |     |      |      |     | 113 |     |
| D                         |     |      |      |     |      |     |     |      |     |      |      |     | 210 |     |
| E                         |     |      |      |     |      |     |     |      |     |      |      |     | 176 |     |
| F                         |     |      |      |     |      |     |     |      |     |      |      |     | 135 |     |
| G                         |     |      | 41   |     | 40   | 1   |     |      |     |      |      |     | 674 |     |
| H                         | 1   |      |      |     |      |     |     |      | 1   |      |      |     | 45  |     |
| I                         | 9   |      |      |     |      | 1   |     |      |     |      |      |     | 282 |     |
| K                         |     |      |      | 3   |      |     |     |      |     |      |      |     | 278 |     |
| L                         | 4   |      |      |     |      |     | 19  |      |     |      |      |     | 540 |     |
| M                         |     |      |      |     |      |     | 9   |      |     |      |      |     | 43  |     |
| N                         |     |      |      |     |      | 1   |     |      |     |      |      |     | 204 |     |
| P                         | 3   |      |      | 2   |      |     |     |      |     |      |      | 2   | 281 |     |
| Q                         |     |      | 29   |     |      |     |     |      |     |      |      |     | 334 |     |
| R                         | 1   |      | 4    |     |      |     | 1   |      |     |      |      |     | 250 |     |
| S                         | 1   |      |      | 1   |      |     |     |      |     |      | 36   | 33  | 986 |     |
| T                         |     |      |      | 1   |      | 33  | 8   |      | 34  |      |      |     | 532 |     |
| V                         | 12  |      |      |     |      |     |     | 36   |     | 36   |      |     | 488 |     |
| W                         |     | 46   |      |     |      |     |     |      |     |      |      |     | 267 |     |
| X                         |     |      |      |     |      |     |     |      |     |      |      |     |     |     |
| Y                         | 16  |      |      |     |      |     |     |      |     |      |      |     | 455 |     |
| Z                         |     |      |      |     |      |     |     |      |     |      |      |     | 1   |     |
| -                         |     |      |      |     |      |     |     |      |     |      |      |     | 466 |     |
| unknown (?)               |     |      |      |     |      |     |     |      |     |      |      |     | 4   |     |
| not sequenced             | 10  | 11   | 16   | 17  | 17   | 20  | 20  | 21   | 21  | 21   | 21   | 22  | 426 |     |
| sum of seq <sup>2</sup>   | 47  | 46   | 41   | 40  | 40   | 37  | 37  | 36   | 36  | 36   | 36   | 35  |     |     |
| oomcaa <sup>1</sup>       | 16  | 46   | 41   | 29  | 40   | 33  | 19  | 36   | 34  | 36   | 36   | 33  |     |     |
| mcaa <sup>4</sup>         | Y   | W    | G    | Q   | G    | T   | L   | V    | T   | V    | S    | S   |     |     |
| rel. oomcaa <sup>5</sup>  | 34% | 100% | 100% | 73% | 100% | 89% | 51% | 100% | 94% | 100% | 100% | 94% |     |     |
| pos occupied <sup>6</sup> | 8   | 1    | 1    | 6   | 1    | 5   | 4   | 1    | 3   | 1    | 1    | 2   |     |     |



Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 53      | 54  | 55  | 56  | 57  | 58  | 59  | 60  | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |
| A                         | 56      |     | 3   | 3   | 3   | 2   | 5   | 4   | 2   | 2   | 4   |     | 2   | 1   |     | 1   | 1   | 12  |     |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |         |     |     |     | 1   |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |
| D                         |         |     | 6   |     | 5   | 5   | 5   | 4   | 3   | 2   | 4   | 3   | 1   |     | 1   | 2   | 1   |     | 41  |
| E                         |         |     | 6   | 1   | 1   | 2   | 1   |     |     | 1   | 3   | 1   | 2   | 1   |     |     |     |     |     |
| F                         |         |     |     | 4   | 1   | 1   |     | 2   | 3   | 2   | 2   |     | 1   | 1   |     |     |     |     | 31  |
| G                         |         |     | 25  | 9   | 10  | 8   | 10  | 11  | 4   | 7   | 7   | 6   | 1   | 1   | 1   | 2   | 1   | 9   |     |
| H                         |         |     | 1   |     |     |     | 1   |     |     |     |     |     | 1   |     |     | 1   |     |     | 2   |
| I                         |         |     |     | 1   |     | 2   | 4   | 1   | 3   | 2   | 3   |     | 1   |     |     |     |     |     | 1   |
| K                         |         |     | 2   | 1   |     |     |     |     |     | 2   | 2   |     |     | 1   |     |     |     |     |     |
| L                         |         |     | 2   | 6   | 7   | 3   | 5   | 3   | 2   | 4   | 1   | 5   | 3   | 3   |     | 1   |     |     |     |
| M                         |         |     |     | 1   | 4   |     | 3   | 1   |     | 2   | 1   |     |     |     |     |     |     |     | 9   |
| N                         |         |     |     | 3   |     |     |     |     | 2   | 1   | 1   | 5   | 1   | 1   |     |     | 2   |     |     |
| P                         |         |     |     | 4   | 5   | 3   | 1   | 1   | 2   | 1   | 1   | 1   | 2   | 3   | 1   | 2   | 1   |     |     |
| Q                         |         |     |     |     | 1   | 1   |     | 1   |     |     | 1   | 1   |     |     | 3   |     |     |     | 1   |
| R                         |         | 54  | 4   | 12  | 2   | 5   | 5   | 3   | 2   | 3   | 1   | 2   |     |     | 2   | 1   |     |     |     |
| S                         |         | 1   | 1   | 4   | 8   | 8   | 1   | 2   | 5   | 7   | 4   | 2   | 1   | 1   | 1   |     |     |     |     |
| T                         |         | 1   | 1   | 2   | 1   | 3   | 4   | 4   | 3   | 3   |     |     | 1   | 1   | 1   |     |     |     |     |
| V                         | 1       | 1   | 4   | 2   | 2   | 5   | 4   | 4   | 7   | 3   | 1   | 2   | 1   |     |     |     |     |     |     |
| W                         |         |     | 1   | 2   | 1   | 2   | 2   | 4   | 5   | 1   | 1   | 2   |     | 2   | 1   |     | 3   | 2   |     |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |         |     |     | 1   | 4   | 5   | 3   | 6   | 4   | 2   | 3   | 4   | 8   | 4   | 8   | 3   | 5   | 8   | 2   |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |         |     |     |     |     | 1   | 2   | 4   | 6   | 9   | 11  | 16  | 23  | 27  | 29  | 34  | 31  | 14  | 4   |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     | 1   | 1   | 1   |
| not sequenced             |         |     | 1   | 1   | 1   | 1   | 1   | 2   | 3   | 3   | 6   | 7   | 8   | 9   | 9   | 10  | 11  | 11  | 11  |
| sum of seq <sup>1</sup>   | 57      | 57  | 56  | 56  | 56  | 56  | 56  | 55  | 54  | 54  | 51  | 50  | 49  | 48  | 48  | 47  | 46  | 46  | 46  |
| oomcaa <sup>1</sup>       | 56      | 54  | 25  | 12  | 10  | 8   | 10  | 11  | 7   | 9   | 11  | 16  | 23  | 27  | 29  | 34  | 31  | 14  | 31  |
| mcaa <sup>1</sup>         | A       | R   | G   | R   | G   | G   | G   | G   | V   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   |
| rel. oomcaa <sup>5</sup>  | 98%     | 95% | 45% | 21% | 18% | 14% | 18% | 20% | 13% | 17% | 22% | 32% | 47% | 56% | 60% | 72% | 67% | 30% | 67% |
| pos occupied <sup>5</sup> | 2       | 4   | 12  | 16  | 16  | 16  | 16  | 16  | 16  | 18  | 18  | 13  | 15  | 13  | 10  | 9   | 8   | 5   | 4   |

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Table 6E: Analysis of V heavy chain subgroup 4

| Framework III             |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
|---------------------------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|------|-----|------|-----|------|--|--|
| amino acid <sup>1</sup>   | 76  | 77  | 78  | 79   | 80  | 81  | 82  | A   | B   | C   | 83  | 84  | 85   | 86   | 87  | 88   | 89  | 90   | 91  | 92   |  |  |
| A                         |     |     |     |      |     |     |     |     |     |     |     | 55  | 57   |      |     | 57   |     |      |     |      |  |  |
| B                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| C                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     | 57   |  |  |
| D                         |     |     |     |      | 1   |     |     |     |     |     |     |     |      | 57   |     |      |     |      |     |      |  |  |
| E                         |     |     |     |      |     | 1   |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| F                         |     |     | 54  |      |     |     |     |     | 1   |     |     |     |      |      |     |      |     |      |     |      |  |  |
| G                         |     |     |     |      |     |     |     | 1   |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| H                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| I                         |     |     | 1   |      |     |     |     | 1   |     |     | 3   |     |      |      |     |      |     |      |     |      |  |  |
| K                         | 3   |     |     |      | 46  |     |     | 2   |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| L                         |     | 3   | 1   |      | 55  |     | 53  |     |     | 2   |     |     |      |      |     |      | 1   |      |     |      |  |  |
| M                         |     |     |     |      |     | 1   | 1   |     |     | 1   |     |     |      |      |     |      | 1   |      |     |      |  |  |
| N                         | 54  |     |     |      |     | 3   |     | 3   | 1   |     |     |     |      |      |     |      |     |      |     |      |  |  |
| P                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| Q                         |     | 54  |     |      | 1   | 1   |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| R                         |     |     |     |      |     | 2   |     | 2   |     |     |     | 1   |      |      |     |      |     |      |     |      |  |  |
| S                         |     |     | 1   | 57   |     | 2   | 1   | 44  | 55  |     | 1   |     |      |      | 2   |      |     |      | 1   |      |  |  |
| T                         |     |     |     |      |     | 1   |     | 4   |     |     | 53  |     |      |      | 55  |      |     |      |     |      |  |  |
| V                         |     |     |     |      |     |     | 2   |     |     | 54  |     | 1   |      |      |     |      | 55  |      |     |      |  |  |
| W                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| X                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| Y                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     | 57   | 56  |      |  |  |
| Z                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| -                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| unknown (?)               |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| not sequenced             |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |  |  |
| sum of seq <sup>1</sup>   | 57  | 57  | 57  | 57   | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57   | 57   | 57  | 57   | 57  | 57   | 57  | 57   |  |  |
| oomcaa <sup>1</sup>       | 54  | 54  | 54  | 57   | 55  | 46  | 53  | 44  | 55  | 54  | 53  | 55  | 57   | 57   | 55  | 57   | 55  | 57   | 56  | 57   |  |  |
| mcaa <sup>1</sup>         | N   | Q   | F   | S    | L   | K   | L   | S   | S   | V   | T   | A   | A    | D    | T   | A    | V   | Y    | Y   | C    |  |  |
| rel. oomcaa <sup>1</sup>  | 95% | 95% | 95% | 100% | 96% | 81% | 93% | 77% | 96% | 95% | 93% | 96% | 100% | 100% | 96% | 100% | 96% | 100% | 98% | 100% |  |  |
| pos occupied <sup>1</sup> | 2   | 2   | 4   | 1    | 3   | 8   | 4   | 7   | 3   | 3   | 3   | 3   | 1    | 1    | 2   | 1    | 3   | 1    | 2   | 1    |  |  |

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Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   | CDR II |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     | 75  |
|---------------------------|--------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 56     | 57  | 58  | 59  | 60  | 61  | 62   | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72  |     |
| A                         |        | 1   |     |     |     |     |      |     |     |     | 1   |     | 1   |     |     | 1   |     | 1   |
| B                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| C                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| D                         |        |     | 2   |     |     |     |      |     |     |     |     | 1   |     |     |     |     | 55  |     |
| E                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |     |
| F                         |        |     |     | 3   |     |     |      |     |     |     |     |     |     |     |     |     |     | 1   |
| G                         | 1      |     |     |     |     |     |      |     |     | 1   |     |     |     |     |     |     |     |     |
| H                         |        |     | 2   |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| I                         | 1      | 1   |     |     |     |     |      |     |     |     |     | 1   | 1   | 48  |     | 3   |     |     |
| K                         |        |     |     |     | 1   |     |      |     | 53  |     |     |     |     |     |     |     | 1   | 51  |
| L                         |        |     |     |     | 1   |     | 55   |     |     |     |     | 1   |     |     |     | 3   |     | 1   |
| M                         |        |     |     |     |     |     |      |     |     |     |     |     |     | 7   |     |     | 2   |     |
| N                         | 2      |     | 40  |     | 53  |     |      |     |     |     |     |     | 2   |     |     |     |     | 1   |
| P                         |        |     |     |     |     | 54  |      | 1   |     |     |     |     |     |     |     |     |     |     |
| Q                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |     |
| R                         | 2      |     |     |     |     |     |      |     | 3   |     | 56  |     |     |     |     |     |     | 2   |
| S                         | 49     |     | 1   |     | 2   |     | 56   |     |     | 56  |     |     | 1   |     | 56  |     | 1   | 57  |
| T                         | 1      | 54  | 1   |     |     | 1   |      |     | 1   |     |     |     | 51  |     | 1   |     | 52  |     |
| V                         | 1      | 1   |     |     |     |     |      |     |     |     |     | 53  |     | 2   |     | 50  |     | 1   |
| W                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| X                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |        |     | 11  | 54  |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| Z                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| -                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| unknown (?)               |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |
| not sequenced             |        |     |     |     | 1   | 1   | 1    | 1   |     |     |     | 1   | 1   |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 57     | 57  | 57  | 57  | 56  | 56  | 56   | 56  | 57  | 57  | 57  | 56  | 56  | 57  | 57  | 57  | 57  | 57  |
| oomcaa <sup>3</sup>       | 49     | 54  | 40  | 54  | 53  | 54  | 56   | 55  | 53  | 56  | 56  | 53  | 51  | 48  | 56  | 50  | 55  | 52  |
| mcaa <sup>4</sup>         | S      | T   | N   | Y   | N   | P   | S    | L   | K   | S   | R   | V   | T   | I   | S   | V   | D   | T   |
| rel. oomcaa <sup>5</sup>  | 86%    | 95% | 70% | 95% | 95% | 96% | 100% | 98% | 93% | 98% | 98% | 95% | 91% | 84% | 98% | 88% | 96% | 91% |
| pos occupied <sup>6</sup> | 7      | 4   | 6   | 2   | 3   | 3   | 1    | 2   | 3   | 2   | 2   | 4   | 5   | 3   | 2   | 4   | 3   | 5   |

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Table 6E: Analysis of V heavy chain subgroup 4

|                           | Framework II |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|------|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41  | 42  | 43  | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A    | B    | C    | 53  | 54  | 55   |  |
| A                         |              |     | 8   | 1   |     |     |     |     |     |     | 1   |     |     |     |      |      |      |     |     |      |  |
| B                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| C                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| D                         |              |     |     |     |     |     |     |     |     |     |     |     |     | 1   |      |      |      | 1   |     |      |  |
| E                         |              |     |     | 1   |     |     |     | 56  |     |     |     | 22  |     |     |      |      |      |     |     |      |  |
| F                         |              |     |     |     |     |     |     |     |     |     |     | 1   |     | 1   |      |      |      |     |     |      |  |
| G                         |              |     |     | 55  |     | 55  |     |     |     |     | 56  | 1   |     |     |      |      |      | 1   |     | 57   |  |
| H                         |              | 2   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 24  |     |      |  |
| I                         |              |     |     |     |     |     |     |     |     | 54  |     | 1   | 54  |     |      |      |      |     |     |      |  |
| K                         |              |     |     |     | 54  |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| L                         |              | 1   |     |     |     |     | 55  |     |     | 2   |     |     |     |     |      |      |      |     |     |      |  |
| M                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| N                         |              |     |     |     |     |     |     |     |     |     |     |     |     | 21  |      |      |      |     |     |      |  |
| P                         |              | 50  | 49  |     |     |     | 2   |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| Q                         | 56           |     |     |     |     |     |     | 1   |     |     |     | 1   |     |     |      |      |      |     |     |      |  |
| R                         |              |     |     |     | 3   | 2   |     |     |     |     |     | 9   |     | 1   |      |      |      |     |     |      |  |
| S                         |              | 3   |     |     |     |     |     |     |     |     |     | 7   |     | 1   |      |      |      |     |     | 52   |  |
| T                         | 1            | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 8   | 5   |      |  |
| V                         |              |     |     |     |     |     |     |     |     | 1   |     |     | 3   |     |      |      |      |     |     |      |  |
| W                         |              |     |     |     |     |     |     | 56  |     |     |     |     |     |     |      |      |      |     |     |      |  |
| X                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| Y                         |              |     |     |     |     |     |     |     | 1   |     |     | 15  |     | 32  |      |      |      |     | 23  |      |  |
| Z                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| -                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     | 57   | 57   | 57   |     |     |      |  |
| unknown (?)               |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| not sequenced             |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |
| sum of seq <sup>2</sup>   | 57           | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57   | 57   | 57   | 57  | 57  | 57   |  |
| oomcaa <sup>3</sup>       | 56           | 50  | 49  | 55  | 54  | 55  | 55  | 56  | 56  | 54  | 56  | 22  | 54  | 32  | 57   | 57   | 57   | 24  | 52  | 57   |  |
| mcaa <sup>4</sup>         | Q            | P   | P   | G   | K   | G   | L   | E   | W   | I   | G   | E   | I   | Y   | -    | -    | -    | H   | S   | G    |  |
| rel. oomcaa <sup>5</sup>  | 98%          | 88% | 86% | 96% | 95% | 96% | 96% | 98% | 98% | 95% | 98% | 39% | 95% | 56% | 100% | 100% | 100% | 42% | 91% | 100% |  |
| pos occupied <sup>6</sup> | 2            | 5   | 2   | 3   | 2   | 2   | 2   | 2   | 2   | 3   | 2   | 8   | 2   | 6   | 1    | 1    | 1    | 5   | 2   | 1    |  |

Table 6E: Analysis of V heavy chain subgroup 4

|                           |      |      |     |      |     |     |     |     |     |     | CDRI |     |     |     |     |      |     |      |     |      |
|---------------------------|------|------|-----|------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|------|-----|------|
| amino acid <sup>1</sup>   | 21   | 22   | 23  | 24   | 25  | 26  | 27  | 28  | 29  | 30  | 31   | A   | B   | 32  | 33  | 34   | 35  | 36   | 37  | 38   |
| A                         |      |      | 22  |      |     |     |     |     |     |     |      |     |     | 1   |     |      |     |      |     |      |
| B                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| C                         |      | 53   |     |      |     |     |     |     |     |     |      |     |     |     | 1   |      |     |      |     |      |
| D                         |      |      | 1   |      |     |     |     |     |     |     | 4    | 1   | 1   | 1   |     |      | 1   |      |     |      |
| E                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| F                         |      |      |     |      | 1   |     |     |     | 22  |     |      |     |     | 1   | 1   |      |     |      | 1   |      |
| G                         |      |      |     |      |     | 53  | 53  |     |     |     | 21   | 3   | 4   |     |     |      | 8   |      |     |      |
| H                         |      |      |     |      |     |     | 1   |     |     |     |      |     |     | 2   |     |      |     |      |     |      |
| I                         |      |      | 1   |      |     |     |     | 1   | 32  |     |      |     |     |     |     |      |     |      | 51  |      |
| K                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| L                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      | 1   |      |
| M                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| N                         |      |      |     |      |     |     |     |     |     | 1   | 1    |     | 2   | 2   |     |      | 1   |      |     |      |
| P                         |      |      |     |      |     |     |     | 3   |     |     |      |     |     |     |     |      |     |      |     |      |
| Q                         |      |      |     |      |     |     |     |     |     |     | 1    |     |     |     |     |      |     |      |     |      |
| R                         |      |      |     |      |     | 1   |     |     |     | 3   | 2    |     | 1   |     |     |      |     |      |     | 57   |
| S                         |      |      | 2   |      | 35  |     |     | 51  | 1   | 52  | 25   | 5   | 9   | 1   |     |      | 44  |      | 1   |      |
| T                         | 53   |      | 29  |      |     |     |     |     |     |     | 2    | 1   |     |     |     |      | 3   |      |     |      |
| V                         |      |      |     | 55   |     | 1   |     |     | 1   |     |      |     |     |     |     |      |     |      | 3   |      |
| W                         |      |      |     |      |     |     |     |     |     |     |      | 1   |     |     | 2   | 56   |     | 57   |     |      |
| X                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| Y                         |      |      |     |      | 19  |     | 1   |     |     |     |      |     |     | 48  | 52  |      |     |      |     |      |
| Z                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| -                         |      |      |     |      |     |     |     |     |     |     |      | 45  | 39  |     |     |      |     |      |     |      |
| unknown (?)               |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| not sequenced             | 4    | 4    | 2   | 2    | 2   | 2   | 2   | 2   | 1   | 1   | 1    |     |     | 1   | 1   | 1    |     |      |     |      |
| sum of seq <sup>2</sup>   | 53   | 53   | 55  | 55   | 55  | 55  | 55  | 55  | 56  | 56  | 56   | 56  | 56  | 56  | 56  | 56   | 57  | 57   | 57  | 57   |
| oomcaa <sup>3</sup>       | 53   | 53   | 29  | 55   | 35  | 53  | 53  | 51  | 32  | 52  | 25   | 45  | 39  | 48  | 52  | 56   | 44  | 57   | 51  | 57   |
| mcaa <sup>4</sup>         | T    | C    | T   | V    | S   | G   | G   | S   | I   | S   | S    | -   | -   | Y   | Y   | W    | S   | W    | I   | R    |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 53% | 100% | 64% | 96% | 96% | 93% | 57% | 93% | 45%  | 80% | 70% | 86% | 93% | 100% | 77% | 100% | 89% | 100% |
| pos occupied <sup>6</sup> | 1    | 1    | 5   | 1    | 3   | 3   | 3   | 3   | 4   | 3   | 7    | 6   | 6   | 7   | 4   | 1    | 5   | 1    | 5   | 1    |

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Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   | Framework I |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
|---------------------------|-------------|-----|-----|------|-----|-----|-----|------|-----|------|------|-----|------|-----|-----|-----|-----|------|-----|-----|
|                           | 1           | 2   | 3   | 4    | 5   | 6   | 7   | 8    | 9   | 10   | 11   | 12  | 13   | 14  | 15  | 16  | 17  | 18   | 19  | 20  |
| A                         |             |     |     |      |     |     |     |      | 19  |      |      |     |      | 1   |     |     | 1   |      | 1   |     |
| B                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| C                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| D                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| E                         |             |     |     |      | 32  |     |     |      |     |      |      |     |      |     |     | 44  |     |      |     |     |
| F                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| G                         |             |     |     |      |     |     | 54  | 1    | 53  |      |      |     |      |     |     | 2   |     |      |     |     |
| H                         |             |     | 4   |      | 2   |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| I                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| K                         |             |     |     |      |     |     |     |      |     |      |      | 1   | 54   |     |     |     |     |      | 1   |     |
| L                         |             | 7   |     | 54   |     |     |     |      |     | 53   | 19   |     |      | 1   |     |     |     | 53   |     | 50  |
| M                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| N                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| P                         |             |     |     |      |     |     |     |      | 33  |      |      |     |      | 51  | 1   |     |     |      |     | 2   |
| Q                         | 52          |     | 50  |      | 51  | 20  |     |      |     |      |      |     |      |     |     | 7   |     |      |     |     |
| R                         | 1           |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| S                         |             |     |     |      |     |     | 33  |      |     |      |      |     |      |     | 52  |     |     |      | 52  |     |
| T                         |             |     |     |      |     |     |     |      | 1   |      |      |     |      |     |     |     | 52  |      |     |     |
| V                         |             | 47  |     |      |     | 1   |     |      |     |      |      | 34  |      |     |     |     |     |      |     | 1   |
| W                         |             |     |     |      |     |     | 20  |      |     |      |      |     |      |     |     |     |     |      |     |     |
| X                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| Y                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| Z                         | 1           |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| -                         |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| unknown (?)               |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| not sequenced             | 3           | 3   | 3   | 3    | 4   | 4   | 4   | 3    | 3   | 4    | 4    | 3   | 3    | 4   | 4   | 4   | 4   | 4    | 3   | 4   |
| sum of seq <sup>2</sup>   | 54          | 54  | 54  | 54   | 53  | 53  | 53  | 54   | 54  | 53   | 53   | 54  | 54   | 53  | 53  | 53  | 53  | 53   | 54  | 53  |
| oomcaa <sup>1</sup>       | 52          | 47  | 50  | 54   | 51  | 32  | 33  | 54   | 33  | 53   | 53   | 34  | 54   | 51  | 52  | 44  | 52  | 53   | 52  | 50  |
| mcaa <sup>1</sup>         | Q           | V   | Q   | L    | Q   | E   | S   | G    | P   | G    | L    | V   | K    | P   | S   | E   | T   | L    | S   | L   |
| rel. oomcaa <sup>5</sup>  | 96%         | 87% | 93% | 100% | 96% | 60% | 62% | 100% | 61% | 100% | 100% | 63% | 100% | 96% | 98% | 83% | 98% | 100% | 96% | 94% |
| pos occupied <sup>6</sup> | 3           | 2   | 2   | 1    | 2   | 3   | 2   | 1    | 4   | 1    | 1    | 3   | 1    | 3   | 2   | 3   | 2   | 1    | 3   | 3   |

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Table 6D: Analysis of V heavy chain subgroup 3

|                           | Framework IV |     |     |     |     |     |     |     |     |     |     |     |      |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|
| amino acid <sup>1</sup>   | 102          | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | sum  |  |
| A                         | 1            |     | 1   |     |     | 2   |     |     |     |     |     |     | 1767 |  |
| B                         |              |     |     | 1   |     |     |     |     |     |     |     |     | 13   |  |
| C                         |              |     |     |     |     |     |     |     |     |     |     |     | 470  |  |
| D                         | 2            |     |     |     |     |     |     |     |     |     |     |     | 112  |  |
| E                         |              |     |     |     | 1   |     |     |     |     |     |     |     | 832  |  |
| F                         | 2            |     |     |     |     |     |     |     |     |     |     |     | 807  |  |
| G                         |              |     | 140 |     | 130 |     | 1   |     |     |     |     |     | 2743 |  |
| H                         | 4            |     |     |     |     |     |     |     |     |     |     |     | 179  |  |
| I                         | 15           |     |     |     |     |     |     |     | 1   | 1   |     |     | 651  |  |
| K                         |              |     |     | 13  |     |     |     |     |     |     |     |     | 933  |  |
| L                         | 10           |     |     | 1   |     |     | 91  |     |     |     |     | 2   | 1881 |  |
| M                         |              |     |     |     |     |     | 6   |     |     |     |     |     | 496  |  |
| N                         | 1            |     |     |     |     | 1   |     |     |     |     |     |     | 844  |  |
| P                         | 17           |     |     |     |     | 1   | 1   |     |     |     |     |     | 568  |  |
| Q                         |              |     |     | 111 |     |     |     |     |     |     |     |     | 949  |  |
| R                         |              |     |     | 8   |     |     |     |     |     |     |     |     | 1413 |  |
| S                         | 7            | 1   |     |     |     |     |     |     |     |     | 118 | 110 | 3009 |  |
| T                         |              |     |     |     |     | 123 | 27  |     | 122 |     |     | 1   | 1426 |  |
| V                         | 34           |     | 1   |     |     | 1   |     | 125 |     | 119 |     |     | 1851 |  |
| W                         |              | 158 |     |     |     |     |     |     |     |     |     |     | 686  |  |
| X                         |              |     |     |     |     |     |     |     |     |     |     |     | 26   |  |
| Y                         | 82           |     |     |     |     |     |     |     |     |     |     |     | 1598 |  |
| Z                         |              |     |     |     |     |     |     |     |     |     |     |     | 8    |  |
| -                         | 9            | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 1   | 1   | 2023 |  |
| unknown (?)               |              |     |     |     |     |     |     |     |     |     |     |     | 12   |  |
| not sequenced             | 27           | 50  | 67  | 75  | 78  | 81  | 83  | 84  | 86  | 89  | 92  | 97  | 1650 |  |
| sum of seq <sup>2</sup>   | 184          | 161 | 144 | 136 | 133 | 130 | 128 | 127 | 125 | 122 | 119 | 114 |      |  |
| oomcaa <sup>3</sup>       | 82           | 158 | 140 | 111 | 130 | 123 | 91  | 125 | 122 | 119 | 118 | 110 |      |  |
| mcaa <sup>4</sup>         | Y            | W   | G   | Q   | G   | T   | L   | V   | T   | V   | S   | S   |      |  |
| rel. oomcaa <sup>5</sup>  | 45%          | 98% | 97% | 82% | 98% | 95% | 71% | 98% | 98% | 98% | 99% | 96% |      |  |
| pos occupied <sup>6</sup> | 12           | 3   | 4   | 6   | 3   | 6   | 6   | 2   | 3   | 3   | 2   | 4   |      |  |

Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 98      | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   | 101 |
| A                         | 7       | 13  | 7   | 9   | 6   | 2   | 3   | 5   | 5   |     | 9   |     | 13  |     | 2   |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         | 13      | 5   |     | 1   | 2   | 11  | 3   |     | 2   |     |     |     |     | 1   |     |
| D                         | 11      | 7   | 10  | 4   | 2   | 3   | 10  | 3   | 3   | 1   |     | 3   | 2   |     | 146 |
| E                         | 6       | 3   | 1   | 13  |     | 1   | 1   |     |     |     |     |     |     |     | 1   |
| F                         | 3       | 5   | 4   | 5   | 5   | 6   | 3   | 5   | 7   | 2   |     | 1   | 1   | 65  | 1   |
| G                         | 34      | 17  | 35  | 17  | 14  | 23  | 10  | 5   | 1   | 5   | 3   | 2   | 32  |     | 6   |
| H                         | 3       | 4   | 3   | 2   | 9   | 2   |     | 1   | 3   | 1   | 2   | 8   | 1   |     |     |
| I                         | 6       | 11  | 4   | 4   | 3   | 1   | 3   | 10  | 3   | 3   | 2   |     | 1   | 2   |     |
| K                         | 2       | 11  |     |     | 3   | 1   |     |     |     |     |     |     |     |     |     |
| L                         | 26      | 13  | 4   | 12  | 8   | 2   | 6   | 3   | 10  | 3   |     |     |     | 2   | 1   |
| M                         |         | 1   | 2   |     |     |     |     |     |     |     | 1   |     |     | 32  |     |
| N                         | 4       | 6   | 4   | 3   | 2   | 2   | 6   |     |     |     | 2   | 5   |     |     | 2   |
| P                         | 6       | 5   | 5   | 6   | 9   | 8   | 2   | 3   | 2   | 1   |     | 3   |     | 9   |     |
| Q                         | 4       |     | 1   | 1   | 1   | 1   | 1   |     |     |     |     | 1   |     |     |     |
| R                         | 4       | 10  | 9   | 7   | 5   | 5   | 2   | 3   | 1   |     | 1   |     | 2   |     | 4   |
| S                         | 16      | 28  | 27  | 25  | 24  | 8   | 11  | 9   | 3   |     | 2   | 3   | 1   | 1   | 1   |
| T                         | 6       | 12  | 9   | 17  | 17  | 1   | 2   | 5   | 1   | 9   | 3   | 1   |     |     |     |
| V                         | 13      | 7   | 15  | 4   | 3   | 6   | 2   | 12  |     | 1   | 1   | 1   | 1   |     |     |
| W                         | 6       | 5   | 6   | 7   | 2   | 4   |     |     |     | 1   |     | 6   | 10  |     |     |
| X                         |         |     |     | 1   |     |     |     |     |     |     |     |     |     |     | 1   |
| Y                         | 16      | 14  | 17  | 5   | 8   | 18  | 20  | 13  | 20  | 25  | 28  | 32  | 28  |     |     |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         | 12      | 21  | 35  | 54  | 73  | 87  | 102 | 110 | 126 | 135 | 134 | 120 | 91  | 71  | 21  |
| unknown (?)               |         |     |     |     |     |     | 3   | 2   | 1   | 1   |     |     | 3   | 2   |     |
| not sequenced             | 14      | 14  | 14  | 14  | 15  | 19  | 21  | 22  | 23  | 23  | 23  | 25  | 25  | 26  | 25  |
| sum of seq <sup>2</sup>   | 198     | 198 | 198 | 197 | 196 | 192 | 190 | 189 | 188 | 188 | 188 | 186 | 186 | 185 | 186 |
| oomcaa <sup>3</sup>       | 34      | 28  | 35  | 54  | 73  | 87  | 102 | 110 | 126 | 135 | 134 | 120 | 91  | 71  | 146 |
| mcaa <sup>4</sup>         | G       | S   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | D   |
| rel. oomcaa <sup>5</sup>  | 17%     | 14% | 18% | 27% | 37% | 45% | 54% | 58% | 67% | 72% | 71% | 65% | 49% | 38% | 78% |
| pos occupied <sup>6</sup> | 20      | 20  | 19  | 20  | 19  | 20  | 17  | 14  | 14  | 12  | 12  | 13  | 12  | 8   | 11  |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | 83  | 84  | 85  | 86  | 87  | 88  | 89  | 90   | 91  | 92   | 93  | 94  | 95  | 96  | 97  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|------|-----|------|-----|-----|-----|-----|-----|
| A                         |     | 149 | 1   |     | 1   | 207 |     |      |     |      | 173 | 2   | 15  | 9   | 11  |
| B                         |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| C                         |     |     |     |     |     |     |     |      | 1   | 210  |     | 5   | 2   |     | 1   |
| D                         |     | 5   | 15  | 209 |     |     |     |      |     |      |     | 2   | 54  | 7   | 6   |
| E                         | 1   |     | 190 |     |     |     |     |      |     |      |     |     | 11  | 2   | 11  |
| F                         |     |     |     |     |     |     | 1   |      | 15  |      |     | 1   |     | 9   | 6   |
| G                         | 1   | 1   | 6   |     |     | 4   | 1   |      |     |      | 2   | 8   | 34  | 26  | 35  |
| H                         |     | 1   |     |     |     |     |     |      | 1   |      |     |     |     | 3   | 11  |
| I                         |     | 8   |     |     |     |     | 2   |      |     |      |     |     | 4   | 15  | 10  |
| K                         | 30  |     |     |     |     |     |     |      |     |      |     | 60  | 4   | 3   | 5   |
| L                         |     |     |     |     |     |     | 18  |      |     |      |     | 1   | 6   | 11  | 7   |
| M                         |     |     |     |     | 2   |     | 1   |      |     |      |     |     |     | 6   | 1   |
| N                         |     | 1   |     | 1   |     |     |     |      |     |      |     | 2   | 20  | 4   | 3   |
| P                         |     | 9   |     |     |     |     |     |      |     |      | 1   | 3   | 4   | 29  | 10  |
| Q                         |     |     |     | 1   |     |     |     |      |     |      |     | 5   | 3   | 9   | 2   |
| R                         | 177 |     |     |     |     |     |     |      |     |      |     | 103 | 9   | 30  | 19  |
| S                         |     | 1   |     |     | 1   |     |     |      |     |      |     | 3   | 9   | 8   | 11  |
| T                         | 3   | 28  |     |     | 207 |     | 1   |      |     |      | 25  | 15  | 7   | 6   | 20  |
| V                         |     | 9   |     |     |     |     | 187 |      |     |      | 10  | 1   | 7   | 7   | 15  |
| W                         |     |     |     |     |     |     |     |      |     | 1    |     |     | 3   | 4   | 3   |
| X                         |     |     |     | 1   |     |     |     |      |     |      |     |     |     |     |     |
| Y                         |     |     |     |     |     |     |     | 211  | 194 |      |     |     | 12  | 9   | 8   |
| Z                         |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| -                         |     |     |     |     |     |     |     |      |     |      |     |     | 1   | 3   | 4   |
| unknown (?)               |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| not sequenced             |     |     |     |     | 1   | 1   | 1   | 1    | 1   | 1    | 1   | 1   | 7   | 12  | 13  |
| sum of seq <sup>2</sup>   | 212 | 212 | 212 | 212 | 211 | 211 | 211 | 211  | 211 | 211  | 211 | 211 | 205 | 200 | 199 |
| oomcaa <sup>3</sup>       | 177 | 149 | 190 | 209 | 207 | 207 | 187 | 211  | 194 | 210  | 173 | 103 | 54  | 30  | 35  |
| mcaa <sup>4</sup>         | R   | A   | E   | D   | T   | A   | V   | Y    | Y   | C    | A   | R   | D   | R   | G   |
| rel. oomcaa <sup>5</sup>  | 83% | 70% | 90% | 99% | 98% | 98% | 89% | 100% | 92% | 100% | 82% | 49% | 26% | 15% | 18% |
| pos occupied <sup>6</sup> | 5   | 10  | 4   | 4   | 4   | 2   | 7   | 1    | 4   | 2    | 5   | 14  | 18  | 20  | 21  |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 71            | 72  | 73  | 74  | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    |
| A                         |               |     |     | 57  |     |     | 1   | 8   |     |     |     |     |     | 1   |      |
| B                         |               |     |     |     |     |     |     |     |     |     | 2   |     |     |     |      |
| C                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| D                         |               | 199 | 38  |     | 2   | 2   |     |     | 1   |     |     |     | 10  |     |      |
| E                         |               | 6   |     |     | 4   |     |     |     |     |     | 5   |     |     |     |      |
| F                         |               |     |     |     |     |     |     |     | 13  |     |     |     |     |     |      |
| G                         |               |     |     |     |     |     |     |     |     |     |     |     | 1   | 4   |      |
| H                         |               |     |     |     |     | 1   |     |     | 1   |     | 2   |     | 2   |     |      |
| I                         |               |     | 1   |     |     |     | 2   | 2   |     |     |     | 3   | 1   | 1   |      |
| K                         |               |     |     |     | 186 | 6   |     |     |     |     |     |     | 3   |     |      |
| L                         |               |     |     |     |     |     |     | 188 |     | 209 |     | 3   | 1   |     | 212  |
| M                         | 1             |     |     |     | 2   |     | 10  | 3   |     | 2   |     | 205 |     |     |      |
| N                         |               | 5   | 170 |     | 2   | 188 |     |     |     |     | 3   |     | 181 | 10  |      |
| P                         |               |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |
| Q                         |               |     |     |     | 7   |     |     |     |     |     | 199 |     |     |     |      |
| R                         | 211           |     |     |     | 1   | 1   |     |     |     |     |     |     | 2   | 8   |      |
| S                         |               |     |     | 153 | 8   | 10  | 56  |     | 3   |     |     |     | 6   | 186 |      |
| T                         |               |     |     |     |     |     | 142 |     |     |     | 1   |     | 4   | 2   |      |
| V                         |               |     |     | 1   |     |     |     | 11  |     | 1   |     | 1   |     |     |      |
| W                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| X                         |               | 2   | 2   |     |     | 4   |     |     |     |     |     |     | 1   |     |      |
| Y                         |               |     |     |     |     |     |     |     | 194 |     |     |     |     |     |      |
| Z                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| -                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| unknown (?)               |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| not sequenced             |               |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     |      |
| sum of seq <sup>2</sup>   | 212           | 212 | 211 | 211 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212  |
| oomcaa <sup>3</sup>       | 211           | 199 | 170 | 153 | 186 | 188 | 142 | 188 | 194 | 209 | 199 | 205 | 181 | 186 | 212  |
| mcaa <sup>4</sup>         | R             | D   | N   | S   | K   | N   | T   | L   | Y   | L   | Q   | M   | N   | S   | L    |
| rel. oomcaa <sup>5</sup>  | 100%          | 94% | 81% | 73% | 88% | 89% | 67% | 89% | 92% | 99% | 94% | 97% | 85% | 88% | 100% |
| pos occupied <sup>6</sup> | 2             | 4   | 4   | 3   | 8   | 7   | 6   | 5   | 5   | 3   | 6   | 4   | 11  | 7   | 1    |

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Table 6D: Analysis of V heavy chain subgroup 3

|                           | CDR II |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65   | 66  | 67  | 68  | 69  | 70   |  |
| A                         | 9      | 1   | 2   |     | 174 | 33  |     |     |     |      |     |     | 1   |     |      |  |
| B                         | 1      | 2   |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| C                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| D                         | 11     |     | 17  |     |     | 160 |     |     |     |      |     |     |     |     |      |  |
| E                         | 8      | 3   | 2   |     |     | 1   |     |     | 2   |      |     |     |     |     |      |  |
| F                         | 1      |     | 3   | 2   |     |     |     |     |     |      |     | 207 |     |     |      |  |
| G                         | 5      | 1   | 5   |     | 4   | 5   |     |     |     | 212  | 1   |     |     |     |      |  |
| H                         | 1      |     | 4   |     |     |     |     |     |     |      |     |     |     |     |      |  |
| I                         | 3      | 37  | 2   |     |     |     |     | 8   |     |      |     |     | 14  | 208 |      |  |
| K                         | 1      | 61  |     |     |     |     |     |     | 199 |      | 8   |     |     |     |      |  |
| L                         | 1      | 1   | 1   |     | 1   |     |     |     |     |      |     | 1   |     | 1   |      |  |
| M                         | 8      |     | 2   |     | 1   |     |     |     |     |      |     |     |     |     |      |  |
| N                         | 51     |     | 4   |     |     | 2   |     |     | 2   |      |     |     |     |     |      |  |
| P                         | 1      | 1   |     |     | 6   | 8   | 18  |     | 1   |      |     |     |     |     |      |  |
| Q                         | 3      | 2   |     |     |     |     |     |     | 2   |      | 2   |     |     |     |      |  |
| R                         | 5      | 4   |     |     | 5   |     |     |     | 6   |      | 201 |     |     |     |      |  |
| S                         | 48     |     | 11  |     | 4   |     | 193 |     |     |      |     | 2   | 7   |     | 211  |  |
| T                         | 42     | 97  | 5   |     | 7   |     |     |     |     |      |     |     | 189 |     | 1    |  |
| V                         |        | 2   |     |     | 10  | 2   |     | 204 |     |      |     | 1   |     | 3   |      |  |
| W                         |        |     | 2   |     |     |     |     |     |     |      |     |     |     |     |      |  |
| X                         | 4      |     | 1   |     |     | 1   |     |     |     |      |     |     |     |     |      |  |
| Y                         | 9      |     | 151 | 210 |     |     | 1   |     |     |      |     | 1   | 1   |     |      |  |
| Z                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| -                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| unknown (?)               |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| not sequenced             |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |  |
| sum of seq <sup>1</sup>   | 212    | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212  | 212 | 212 | 212 | 212 | 212  |  |
| oomcaa <sup>3</sup>       | 51     | 97  | 151 | 210 | 174 | 160 | 193 | 204 | 199 | 212  | 201 | 207 | 189 | 208 | 211  |  |
| mcaa <sup>4</sup>         | N      | T   | Y   | Y   | A   | D   | S   | V   | K   | G    | R   | F   | T   | I   | S    |  |
| rel. oomcaa <sup>5</sup>  | 24%    | 46% | 71% | 99% | 82% | 75% | 91% | 96% | 94% | 100% | 95% | 98% | 89% | 98% | 100% |  |
| pos occupied <sup>6</sup> | 19     | 12  | 15  | 2   | 9   | 8   | 3   | 2   | 6   | 1    | 4   | 5   | 5   | 3   | 2    |  |

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Table 6D: Analysis of V heavy chain subgroup 3

| work II                   |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 44  | 45   | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A   | B   | C   | 53  | 54  | 55  |
| A                         | 1   |      |     |     |     | 77  | 42  |     | 1   | 2   |     | 14  |     | 7   |     |
| B                         |     |      | 3   |     |     |     |     |     |     | 1   |     |     |     |     |     |
| C                         |     |      |     |     |     |     |     |     |     |     |     |     | 1   |     |     |
| D                         |     |      | 1   |     |     |     |     |     |     | 7   |     |     | 94  | 8   | 3   |
| E                         |     |      | 198 |     |     |     |     |     | 3   | 2   | 1   |     | 2   |     | 1   |
| F                         |     |      |     |     |     |     | 7   | 1   | 2   | 1   |     |     |     | 1   | 8   |
| G                         | 207 |      |     |     |     | 33  | 11  |     | 10  | 46  |     |     | 4   | 163 | 85  |
| H                         |     |      |     |     |     |     | 6   |     |     | 1   |     |     |     |     |     |
| I                         |     |      |     |     | 3   |     | 3   | 191 |     | 1   |     |     |     |     | 1   |
| K                         |     |      |     |     |     |     |     | 1   | 37  | 2   | 30  |     | 3   | 1   |     |
| L                         |     | 211  |     |     | 5   |     | 12  | 1   |     |     |     |     |     |     |     |
| M                         |     |      |     |     |     |     | 1   | 1   |     |     |     |     |     |     |     |
| N                         |     |      |     |     |     |     | 13  |     | 7   | 9   | 2   |     | 13  | 11  | 1   |
| P                         |     | 1    |     |     |     |     |     |     |     | 1   |     |     | 1   |     |     |
| Q                         |     |      | 7   |     |     |     | 7   |     |     | 10  |     |     |     |     |     |
| R                         | 1   |      |     |     |     | 24  | 1   | 17  | 5   | 1   |     |     | 2   |     | 16  |
| S                         | 3   |      |     | 1   |     | 102 | 11  | 9   | 118 | 43  |     | 1   | 74  | 17  | 82  |
| T                         |     |      |     |     |     |     | 3   | 5   | 4   | 2   |     | 13  | 12  | 3   | 3   |
| V                         |     |      | 3   |     | 204 |     | 49  | 2   |     | 1   |     | 6   |     |     |     |
| W                         |     |      |     | 210 |     |     | 1   |     | 8   | 6   |     |     |     |     |     |
| X                         |     |      |     |     |     |     |     |     |     |     |     |     | 4   |     | 3   |
| Y                         |     |      |     | 1   |     |     | 22  |     | 5   | 58  |     |     |     |     | 8   |
| Z                         |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |     |      |     |     |     |     |     |     |     | 14  | 178 | 178 | 2   | 1   | 1   |
| unknown (?)               |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| not sequenced             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 212 | 212  | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 |
| oomcaa <sup>3</sup>       | 207 | 211  | 198 | 210 | 204 | 102 | 49  | 191 | 118 | 58  | 178 | 178 | 94  | 163 | 85  |
| mcaa <sup>4</sup>         | G   | L    | E   | W   | V   | S   | V   | I   | S   | Y   | -   | -   | D   | G   | G   |
| rel. oomcaa <sup>5</sup>  | 98% | 100% | 93% | 99% | 96% | 48% | 23% | 90% | 56% | 27% | 84% | 84% | 44% | 77% | 40% |
| pos occupied <sup>6</sup> | 4   | 2    | 5   | 3   | 3   | 3   | 15  | 9   | 11  | 19  | 5   | 5   | 12  | 9   | 12  |

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Table 6D: Analysis of V heavy chain subgroup 3

|                           | CDRI |      |      |     |     |     |     |      |     |     | Frame |     |     |     |     |
|---------------------------|------|------|------|-----|-----|-----|-----|------|-----|-----|-------|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38  | 39    | 40  | 41  | 42  | 43  |
| A                         | 1    |      |      | 17  | 80  |     | 1   |      |     | 1   |       | 187 |     | 1   |     |
| B                         |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |
| C                         |      |      |      |     |     |     |     |      |     |     |       | 1   |     | 1   |     |
| D                         | 26   |      |      | 3   | 7   |     | 2   |      |     |     |       |     |     |     |     |
| E                         | 1    |      |      |     | 10  |     |     |      |     |     |       |     |     | 1   | 1   |
| F                         |      |      |      | 5   |     |     |     |      |     |     |       |     |     |     |     |
| G                         | 13   |      |      |     | 31  |     | 1   |      |     |     |       | 2   |     | 209 |     |
| H                         |      |      |      | 4   |     |     | 88  |      |     |     |       |     |     |     |     |
| I                         | 1    |      |      | 1   |     | 15  |     |      | 12  |     |       |     |     |     |     |
| K                         | 7    |      |      |     |     |     |     |      |     |     | 1     |     |     |     | 202 |
| L                         | 3    |      |      |     |     | 3   |     |      | 2   | 3   | 1     | 2   | 1   |     |     |
| M                         |      |      |      |     |     | 193 |     |      |     |     |       |     |     |     |     |
| N                         | 35   |      |      | 8   | 3   |     | 34  |      |     |     |       |     |     |     |     |
| P                         |      |      |      | 1   |     |     | 1   |      |     |     |       | 4   | 191 |     |     |
| Q                         |      |      |      |     |     |     |     |      |     |     | 209   |     | 1   |     | 1   |
| R                         | 7    |      |      |     |     |     |     |      |     | 207 |       | 7   |     |     | 8   |
| S                         | 103  |      |      | 17  | 8   |     | 72  |      |     |     |       | 3   | 14  |     |     |
| T                         | 9    |      |      |     | 15  |     | 10  |      |     |     |       | 4   | 5   |     |     |
| V                         | 2    |      |      |     | 7   | 1   |     |      | 197 |     |       | 2   |     |     |     |
| W                         |      |      |      |     | 30  |     |     | 212  |     |     |       |     |     |     |     |
| X                         | 1    |      |      |     |     |     |     |      |     |     |       |     |     |     |     |
| Y                         | 1    |      |      | 154 | 19  |     | 3   |      |     |     |       |     |     |     |     |
| Z                         |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |
| -                         |      | 210  | 210  |     |     |     |     |      |     |     |       |     |     |     |     |
| unknown (?)               |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |
| not sequenced             | 2    |      |      | 2   | 2   |     |     |      | 1   | 1   | 1     |     |     |     |     |
| sum of seq <sup>2</sup>   | 210  | 210  | 210  | 210 | 210 | 212 | 212 | 212  | 211 | 211 | 211   | 212 | 212 | 212 | 212 |
| oomcaa <sup>1</sup>       | 103  | 210  | 210  | 154 | 80  | 193 | 88  | 212  | 197 | 207 | 209   | 187 | 191 | 209 | 202 |
| mcaa <sup>1</sup>         | S    | -    | -    | Y   | A   | M   | H   | W    | V   | R   | Q     | A   | P   | G   | K   |
| rel. oomcaa <sup>5</sup>  | 49%  | 100% | 100% | 73% | 38% | 91% | 42% | 100% | 93% | 98% | 99%   | 88% | 90% | 99% | 95% |
| pos occupied <sup>6</sup> | 14   | 1    | 1    | 9   | 10  | 4   | 9   | 1    | 3   | 3   | 3     | 9   | 5   | 4   | 4   |

Table 6D: Analysis of V heavy chain subgroup 3

| work I                    |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
|---------------------------|-----|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|-----|-----|-----|----|
| amino acid <sup>1</sup>   | 16  | 17  | 18  | 19  | 20  | 21  | 22   | 23  | 24  | 25   | 26  | 27  | 28  | 29  | 30  |    |
| A                         |     |     |     |     |     |     |      | 183 | 192 |      | 1   |     |     |     |     |    |
| B                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| C                         |     |     |     |     |     | 1   | 209  |     |     |      |     |     |     |     |     |    |
| D                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     | 7   |    |
| E                         | 8   |     |     |     |     |     |      | 8   |     |      | 3   |     | 1   |     |     |    |
| F                         |     | 1   | 1   |     |     | 1   |      |     |     |      |     | 201 |     | 201 |     |    |
| G                         | 134 |     |     |     |     |     |      |     | 2   |      | 207 |     |     |     |     | 3  |
| H                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     | 1  |
| I                         |     |     |     |     |     |     |      | 2   |     |      |     | 3   | 17  | 1   |     |    |
| K                         |     |     |     | 15  |     |     |      |     |     |      |     |     |     |     |     | 4  |
| L                         |     |     | 205 |     | 201 |     |      |     |     |      |     | 6   |     | 3   |     |    |
| M                         |     |     | 1   |     |     |     |      |     |     |      |     |     | 1   |     |     |    |
| N                         |     |     |     |     |     |     |      |     |     |      |     |     | 10  |     | 10  |    |
| P                         |     |     |     |     |     |     |      | 1   |     |      |     |     | 2   |     |     |    |
| Q                         |     |     | 1   |     |     |     |      |     |     |      |     |     |     |     |     |    |
| R                         | 62  |     |     | 191 |     |     |      |     |     |      |     |     |     |     |     | 11 |
| S                         |     | 206 |     |     |     | 207 |      | 4   | 2   | 209  |     |     | 15  |     | 174 |    |
| T                         | 4   | 1   |     | 2   |     |     |      | 4   | 4   |      |     | 1   | 163 |     |     |    |
| V                         |     |     |     |     | 8   |     |      | 7   | 9   |      |     |     | 1   | 6   |     |    |
| W                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| X                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| Y                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| Z                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| -                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| unknown (?)               |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |    |
| not sequenced             | 4   | 4   | 4   | 4   | 3   | 3   | 3    | 3   | 3   | 3    | 1   | 1   | 2   | 1   | 2   |    |
| sum of seq <sup>2</sup>   | 208 | 208 | 208 | 208 | 209 | 209 | 209  | 209 | 209 | 209  | 211 | 211 | 210 | 211 | 210 |    |
| oomcaa <sup>3</sup>       | 134 | 206 | 205 | 191 | 201 | 207 | 209  | 183 | 192 | 209  | 207 | 201 | 163 | 201 | 174 |    |
| mcaa <sup>4</sup>         | G   | S   | L   | R   | L   | S   | C    | A   | A   | S    | G   | F   | T   | F   | S   |    |
| rel. oomcaa <sup>5</sup>  | 64% | 99% | 99% | 92% | 96% | 99% | 100% | 88% | 92% | 100% | 98% | 95% | 78% | 95% | 83% |    |
| pos occupied <sup>6</sup> | 4   | 3   | 4   | 3   | 2   | 3   | 1    | 7   | 5   | 1    | 3   | 4   | 8   | 4   | 7   |    |

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Table 6D: Analysis of V heavy chain subgroup 3

|                           | Frame |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
|---------------------------|-------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 1     | 2   | 3   | 4   | 5   | 6   | 7   | 8    | 9   | 10  | 11  | 12  | 13  | 14  | 15  |
| A                         |       |     |     |     | 1   |     | 1   |      |     | 12  |     | 1   |     | 3   | 1   |
| B                         |       |     | 1   |     |     | 1   |     |      |     |     |     |     | 1   |     |     |
| C                         |       |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| D                         | 1     |     |     |     |     | 1   |     |      |     | 16  |     |     |     |     |     |
| E                         | 110   |     | 9   |     | 15  | 166 |     |      | 9   |     |     |     | 8   |     | 2   |
| F                         |       |     |     |     |     |     |     |      |     |     | 4   |     |     |     |     |
| G                         |       |     |     |     |     |     |     | 181  | 193 | 174 |     | 1   |     |     | 202 |
| H                         |       |     | 5   |     |     |     |     |      |     |     |     |     | 4   |     |     |
| I                         |       |     |     |     |     |     |     |      |     |     |     | 9   |     |     |     |
| K                         |       | 5   | 3   |     |     |     |     |      |     |     |     |     | 26  |     |     |
| L                         |       | 1   | 5   | 176 | 43  |     |     |      |     |     | 140 |     |     | 1   |     |
| M                         |       | 12  |     | 1   |     |     |     |      |     |     |     |     |     |     |     |
| N                         |       |     |     |     |     |     |     |      |     | 1   |     |     |     |     |     |
| P                         |       |     |     |     |     |     |     |      |     |     |     |     | 1   | 194 |     |
| Q                         | 41    |     | 138 | 1   | 3   | 12  |     |      |     |     |     |     | 162 |     |     |
| R                         |       |     | 6   |     |     |     |     |      |     |     |     |     | 4   |     |     |
| S                         |       |     |     |     |     |     | 178 |      |     | 2   |     |     |     | 8   |     |
| T                         |       |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| V                         | 5     | 147 |     | 1   | 118 |     |     |      |     |     | 62  | 195 |     |     |     |
| W                         |       |     |     |     |     |     |     |      |     |     |     |     |     |     | 1   |
| X                         |       |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Y                         |       |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Z                         | 8     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| -                         |       |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| unknown (?)               |       |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| not sequenced             | 47    | 47  | 45  | 33  | 32  | 32  | 32  | 31   | 10  | 7   | 6   | 6   | 6   | 6   | 6   |
| sum of seq <sup>2</sup>   | 165   | 165 | 167 | 179 | 180 | 180 | 180 | 181  | 202 | 205 | 206 | 206 | 206 | 206 | 206 |
| oomcaa <sup>3</sup>       | 110   | 147 | 138 | 176 | 118 | 166 | 178 | 181  | 193 | 174 | 140 | 195 | 162 | 194 | 202 |
| mcaa <sup>4</sup>         | E     | V   | Q   | L   | V   | E   | S   | G    | G   | G   | L   | V   | Q   | P   | G   |
| rel. oomcaa <sup>5</sup>  | 67%   | 89% | 83% | 98% | 66% | 92% | 99% | 100% | 96% | 85% | 68% | 95% | 79% | 94% | 98% |
| pos occupied <sup>6</sup> | 5     | 4   | 7   | 4   | 5   | 4   | 3   | 1    | 2   | 5   | 3   | 4   | 7   | 4   | 4   |

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Table 6C: Analysis of V heavy chain subgroup 2

| amino acid <sup>1</sup>   | Framework IV |      |      |     |      |      |     |      |     |      |      |      | sum |
|---------------------------|--------------|------|------|-----|------|------|-----|------|-----|------|------|------|-----|
|                           | 102          | 103  | 104  | 105 | 106  | 107  | 108 | 109  | 110 | 111  | 112  | 113  |     |
| A                         |              |      |      |     |      |      |     |      | 1   |      |      |      | 35  |
| B                         |              |      |      |     |      |      |     |      |     |      |      |      |     |
| C                         |              |      |      |     |      |      |     |      |     |      |      |      | 16  |
| D                         |              |      |      |     |      |      |     |      |     |      |      |      | 43  |
| E                         |              |      |      |     |      |      |     |      |     |      |      |      | 21  |
| F                         |              |      |      |     |      |      |     |      |     |      |      |      | 18  |
| G                         |              |      | 6    |     | 6    |      |     |      |     |      |      |      | 55  |
| H                         |              |      |      |     |      |      |     |      |     |      |      |      | 6   |
| I                         |              |      |      |     |      |      |     |      |     |      |      |      | 29  |
| K                         |              |      |      | 1   |      |      | 1   |      |     |      |      |      | 42  |
| L                         | 1            |      |      |     |      |      | 3   |      |     |      |      |      | 78  |
| M                         |              |      |      |     |      |      |     |      |     |      |      |      | 20  |
| N                         |              |      |      |     |      |      |     |      |     |      |      |      | 23  |
| P                         | 1            |      |      |     |      |      | 1   |      |     |      |      |      | 41  |
| Q                         |              |      |      | 3   |      |      |     |      |     |      |      |      | 23  |
| R                         |              |      |      | 2   |      |      |     |      |     |      |      |      | 41  |
| S                         |              |      |      |     |      |      |     |      |     |      | 6    | 3    | 82  |
| T                         |              |      |      |     |      | 6    | 1   |      | 5   |      |      |      | 102 |
| V                         | 3            |      |      |     |      |      |     | 6    |     | 6    |      |      | 68  |
| W                         |              | 6    |      |     |      |      |     |      |     |      |      |      | 29  |
| X                         |              |      |      |     |      |      |     |      |     |      |      |      | 4   |
| Y                         | 1            |      |      |     |      |      |     |      |     |      |      |      | 35  |
| Z                         |              |      |      |     |      |      |     |      |     |      |      |      | 3   |
| -                         |              |      |      |     |      |      |     |      |     |      |      |      | 56  |
| unknown (?)               |              |      |      |     |      |      |     |      |     |      |      |      |     |
| not sequenced             | 1            | 1    | 1    | 1   | 1    | 1    | 1   | 1    | 1   | 1    | 1    | 4    | 54  |
| sum of seq <sup>2</sup>   | 6            | 6    | 6    | 6   | 6    | 6    | 6   | 6    | 6   | 6    | 6    | 3    |     |
| oomcaa <sup>3</sup>       | 3            | 6    | 6    | 3   | 6    | 6    | 3   | 6    | 5   | 6    | 6    | 3    |     |
| mcaa <sup>4</sup>         | V            | W    | G    | Q   | G    | T    | L   | V    | T   | V    | S    | S    |     |
| rel. oomcaa <sup>5</sup>  | 50%          | 100% | 100% | 50% | 100% | 100% | 50% | 100% | 83% | 100% | 100% | 100% |     |
| pos occupied <sup>6</sup> | 4            | 1    | 1    | 3   | 1    | 1    | 4   | 1    | 2   | 1    | 1    | 1    |     |

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Table 6C: Analysis of V heavy chain subgroup 2

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|------|
|                           | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H    | I   | J   | K    |
| A                         | 5       |     |     |     |     |     |     | 1   | 2   | 1   |     |     |     |     |     |      |     |     |      |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| C                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| D                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     | 6    |
| E                         |         |     |     |     |     |     |     | 2   |     |     | 1   |     |     |     |     |      |     |     |      |
| F                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     | 3   |      |
| G                         |         |     |     |     |     | 1   | 1   |     | 1   | 2   | 1   | 1   | 1   | 1   |     |      |     |     |      |
| H                         |         | 1   |     | 1   |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| I                         |         |     | 3   |     |     | 2   |     |     |     |     |     |     |     |     |     |      |     |     |      |
| K                         |         |     |     |     |     |     | 1   |     |     |     |     |     |     |     |     |      |     |     |      |
| L                         |         |     |     |     |     |     |     | 1   |     | 1   |     |     |     |     |     |      |     | 1   |      |
| M                         |         |     |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |     | 2   |      |
| N                         |         |     |     | 1   | 2   |     |     |     |     |     |     |     |     |     |     |      | 1   |     |      |
| P                         |         |     |     | 1   | 1   |     | 1   |     | 1   |     |     |     |     |     |     |      |     |     |      |
| Q                         |         |     | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| R                         |         | 6   | 1   |     |     | 1   |     |     | 1   |     |     |     |     |     |     |      |     |     |      |
| S                         |         |     |     | 1   |     | 1   | 1   |     |     |     |     |     |     |     |     |      |     |     |      |
| T                         |         |     |     | 1   |     |     | 1   |     | 1   |     |     |     |     |     |     |      |     |     |      |
| V                         | 2       |     | 1   | 1   | 1   |     | 1   | 1   |     |     | 1   |     |     |     |     |      |     |     |      |
| W                         |         |     |     |     |     | 1   |     |     |     |     |     |     |     |     | 1   |      |     | 1   |      |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| Y                         |         |     |     |     | 2   |     |     |     |     |     | 1   | 2   | 1   | 1   | 1   |      |     | 2   |      |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| -                         |         |     |     |     |     |     |     |     | 2   | 2   | 3   | 4   | 4   | 4   | 4   | 6    | 5   | 3   |      |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |      |
| not sequenced             |         |     | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1   | 1   | 1    |
| sum of seq <sup>2</sup>   | 7       | 7   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6    | 6   | 6   | 6    |
| oomcaa <sup>3</sup>       | 5       | 6   | 3   | 1   | 2   | 2   | 1   | 2   | 2   | 2   | 2   | 3   | 4   | 4   | 4   | 6    | 5   | 3   | 6    |
| mcaa <sup>4</sup>         | A       | R   | I   | H   | N   | I   | G   | E   | A   | -   | -   | -   | -   | -   | -   | -    | -   | F   | D    |
| rel. oomcaa <sup>5</sup>  | 71%     | 86% | 50% | 17% | 33% | 33% | 17% | 33% | 33% | 33% | 33% | 50% | 67% | 67% | 67% | 100% | 83% | 50% | 100% |
| pos occupied <sup>6</sup> | 2       | 2   | 4   | 6   | 4   | 5   | 6   | 5   | 5   | 4   | 5   | 3   | 3   | 3   | 3   | 1    | 2   | 3   | 1    |

Table 6C: Analysis of V heavy chain subgroup 2

| Framework III             |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
|---------------------------|-----|------|------|------|-----|-----|------|-----|-----|-----|-----|------|-----|------|------|-----|------|------|------|------|
| amino acid <sup>1</sup>   | 76  | 77   | 78   | 79   | 80  | 81  | 82   | A   | B   | C   | 83  | 84   | 85  | 86   | 87   | 88  | 89   | 90   | 91   | 92   |
| A                         |     |      |      |      |     |     |      |     |     |     |     |      | 1   |      |      | 5   |      |      |      |      |
| B                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| C                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      | 7    |
| D                         |     |      |      |      |     |     |      |     |     |     | 6   |      |     | 7    |      |     |      |      |      |      |
| E                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| F                         |     |      |      |      | 1   |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| G                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      | 2   |      |      |      |      |
| H                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| I                         |     |      |      |      |     | 2   |      | 1   |     |     |     |      |     |      |      |     |      |      |      |      |
| K                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| L                         |     |      |      |      | 6   |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| M                         |     |      |      |      |     |     | 7    |     |     | 5   |     |      |     |      |      |     |      |      |      |      |
| N                         | 5   |      |      |      |     |     |      |     | 6   |     | 1   |      |     |      |      |     |      |      |      |      |
| P                         |     |      |      |      |     |     |      |     |     |     |     | 7    |     |      |      |     |      |      |      |      |
| Q                         |     | 7    |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| R                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| S                         | 2   |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| T                         |     |      |      |      |     | 5   |      | 5   |     |     |     |      |     |      | 7    |     | 7    |      |      |      |
| V                         |     |      | 7    | 7    |     |     |      |     |     | 1   |     |      | 6   |      |      |     |      |      |      |      |
| W                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| X                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| Y                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      | 7    | 7    |      |
| Z                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| -                         |     |      |      |      |     |     |      | 1   | 1   | 1   |     |      |     |      |      |     |      |      |      |      |
| unknown (?)               |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| not sequenced             |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| sum of seq <sup>2</sup>   | 7   | 7    | 7    | 7    | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7    | 7    | 7   | 7    | 7    | 7    | 7    |
| oomcaa <sup>3</sup>       | 5   | 7    | 7    | 7    | 6   | 5   | 7    | 5   | 6   | 5   | 6   | 7    | 6   | 7    | 7    | 5   | 7    | 7    | 7    | 7    |
| mcaa <sup>4</sup>         | N   | Q    | V    | V    | L   | T   | M    | T   | N   | M   | D   | P    | V   | D    | T    | A   | T    | Y    | Y    | C    |
| rel. oomcaa <sup>5</sup>  | 71% | 100% | 100% | 100% | 86% | 71% | 100% | 71% | 86% | 71% | 86% | 100% | 86% | 100% | 100% | 71% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 2   | 1    | 1    | 1    | 2   | 2   | 1    | 3   | 2   | 3   | 2   | 1    | 2   | 1    | 1    | 2   | 1    | 1    | 1    | 1    |

Table 6C: Analysis of V heavy chain subgroup 2

|                           | CDR II |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
|---------------------------|--------|-----|-----|-----|-----|-----|------|------|-----|-----|------|------|-----|-----|-----|-----|-----|-----|------|-----|--|--|--|--|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62   | 63   | 64  | 65  | 66   | 67   | 68  | 69  | 70  | 71  | 72  | 73  | 74   | 75  |  |  |  |  |  |
| A                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| B                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| C                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| D                         | 5      |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     | 6   | 1   |      |     |  |  |  |  |  |
| E                         | 1      |     |     |     |     |     |      |      | 1   |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| F                         |        | 1   |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| G                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| H                         |        |     |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| I                         |        |     |     |     |     |     |      |      |     |     |      |      |     | 6   |     |     |     |     |      |     |  |  |  |  |  |
| K                         | 1      | 6   |     |     |     |     |      |      | 4   |     |      |      |     |     |     | 6   |     |     |      | 6   |  |  |  |  |  |
| L                         |        |     |     |     |     |     |      | 7    |     |     |      | 7    |     |     |     |     |     |     |      |     |  |  |  |  |  |
| M                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| N                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     | 1   |     |      |     |  |  |  |  |  |
| P                         |        |     |     |     |     | 2   |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Q                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| R                         |        |     | 2   |     |     | 1   |      |      | 2   | 7   |      |      |     |     |     | 1   |     |     |      | 1   |  |  |  |  |  |
| S                         |        |     | 2   |     | 6   |     | 7    |      |     | 4   |      |      | 1   |     | 5   |     |     |     | 7    |     |  |  |  |  |  |
| T                         |        |     |     |     |     | 4   |      |      |     | 3   |      |      | 6   |     | 2   |     |     | 6   |      |     |  |  |  |  |  |
| V                         |        |     |     |     |     |     |      |      |     |     |      |      |     | 1   |     |     |     |     |      |     |  |  |  |  |  |
| W                         |        |     |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| X                         |        |     |     |     | 1   |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Y                         |        |     | 3   | 4   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Z                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| -                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| unknown (?)               |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| not sequenced             |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 7      | 7   | 7   | 7   | 7   | 7   | 7    | 7    | 7   | 7   | 7    | 7    | 7   | 7   | 7   | 7   | 7   | 7   | 7    | 7   |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 5      | 6   | 3   | 4   | 6   | 4   | 7    | 7    | 4   | 4   | 7    | 7    | 6   | 6   | 5   | 6   | 6   | 6   | 7    | 6   |  |  |  |  |  |
| mcaa <sup>4</sup>         | D      | K   | Y   | Y   | S   | T   | S    | L    | K   | S   | R    | L    | T   | I   | S   | K   | D   | T   | S    | K   |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 71%    | 86% | 43% | 57% | 86% | 57% | 100% | 100% | 57% | 57% | 100% | 100% | 86% | 86% | 71% | 86% | 86% | 86% | 100% | 86% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 3      | 2   | 3   | 4   | 2   | 3   | 1    | 1    | 3   | 2   | 1    | 1    | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 2   |  |  |  |  |  |

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Table 6C: Analysis of V heavy chain subgroup 2

|                           | Framework II |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
|---------------------------|--------------|-----|------|------|-----|-----|------|------|------|------|------|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41   | 42   | 43  | 44  | 45   | 46   | 47   | 48   | 49   | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              |     |      |      |     | 6   |      |      |      |      |      | 7   |     |     |     |      |      |     |     |     |  |  |  |  |
| B                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| C                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| D                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 2   |     |      |      |     | 3   | 6   |  |  |  |  |
| E                         |              |     |      |      |     |     |      | 7    |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| F                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 2   |     |      |      |     |     |     |  |  |  |  |
| G                         |              | 1   |      | 7    |     | 1   |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| H                         |              |     |      |      |     |     |      |      |      |      |      | 2   |     |     |     |      |      |     |     | 1   |  |  |  |  |
| I                         |              |     |      |      |     |     |      |      |      |      |      |     | 6   |     |     |      |      |     |     |     |  |  |  |  |
| K                         |              |     |      |      | 6   |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| L                         |              |     |      |      |     |     | 7    |      |      | 7    |      | 2   | 1   | 1   |     |      |      |     |     |     |  |  |  |  |
| M                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| N                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     | 3   |     |  |  |  |  |
| P                         |              | 5   | 7    |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| Q                         | 6            |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| R                         | 1            |     |      |      | 1   |     |      |      |      |      |      | 2   |     |     |     |      |      |     |     |     |  |  |  |  |
| S                         |              | 1   |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      | 2   |     |     |  |  |  |  |
| T                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| V                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| W                         |              |     |      |      |     |     |      |      | 7    |      |      | 1   |     |     |     |      |      |     | 4   |     |  |  |  |  |
| X                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 1   |     |      |      | 1   | 1   |     |  |  |  |  |
| Y                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 1   | 1   |      |      |     |     |     |  |  |  |  |
| Z                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| -                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     | 6   | 7    | 7    |     |     |     |  |  |  |  |
| unknown (?)               |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| not sequenced             |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 7            | 7   | 7    | 7    | 7   | 7   | 7    | 7    | 7    | 7    | 7    | 7   | 7   | 7   | 7   | 7    | 7    | 7   | 7   | 7   |  |  |  |  |
| oomcaa <sup>3</sup>       | 6            | 5   | 7    | 7    | 6   | 6   | 7    | 7    | 7    | 7    | 7    | 2   | 6   | 2   | 6   | 7    | 7    | 4   | 3   | 6   |  |  |  |  |
| mcaa <sup>4</sup>         | Q            | P   | P    | G    | K   | A   | L    | E    | W    | L    | A    | H   | I   | D   | -   | -    | -    | W   | D   | D   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 86%          | 71% | 100% | 100% | 86% | 86% | 100% | 100% | 100% | 100% | 100% | 29% | 86% | 29% | 86% | 100% | 100% | 57% | 43% | 86% |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 3   | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 4   | 2   | 5   | 2   | 1    | 1    | 3   | 3   | 2   |  |  |  |  |

Table 6C: Analysis of V heavy chain subgroup 2

|                           |      |      |     |     |     |      |     |     |     |     | CDRI |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
|---------------------------|------|------|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|------|------|------|--|--|--|--|--|--|--|
| amino acid <sup>1</sup>   | 21   | 22   | 23  | 24  | 25  | 26   | 27  | 28  | 29  | 30  | 31   | A   | B   | 32  | 33  | 34   | 35  | 36   | 37   | 38   |  |  |  |  |  |  |  |
| A                         |      |      |     |     |     |      |     | 1   |     |     |      | 1   |     |     | 1   |      |     |      |      |      |  |  |  |  |  |  |  |
| B                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| C                         |      | 7    |     |     |     |      |     |     |     |     |      |     |     |     | 2   |      |     |      |      |      |  |  |  |  |  |  |  |
| D                         |      |      |     |     |     |      |     |     |     |     |      | 1   |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| E                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| F                         |      |      |     | 3   |     |      | 6   |     | 1   |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| G                         |      |      |     |     |     | 7    |     |     |     |     |      |     | 4   |     | 3   |      | 3   |      |      |      |  |  |  |  |  |  |  |
| H                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| I                         |      |      |     |     |     |      |     |     |     |     |      |     | 1   |     |     |      |     |      | 7    |      |  |  |  |  |  |  |  |
| K                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| L                         |      |      |     | 2   |     |      | 1   |     | 6   |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| M                         |      |      |     |     |     |      |     |     |     |     |      |     |     | 5   |     |      |     |      |      |      |  |  |  |  |  |  |  |
| N                         |      |      |     |     |     |      |     |     |     |     | 2    |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| P                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| Q                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| R                         |      |      |     |     |     |      |     |     |     |     |      |     | 2   |     | 1   |      |     |      |      | 7    |  |  |  |  |  |  |  |
| S                         |      |      | 1   |     | 6   |      |     | 6   |     | 6   | 2    | 4   |     |     |     |      | 4   |      |      |      |  |  |  |  |  |  |  |
| T                         | 6    | 6    |     |     |     |      |     |     |     | 1   | 3    | 1   |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| V                         |      |      |     | 2   |     |      |     |     |     |     |      |     |     | 2   |     | 7    |     |      |      |      |  |  |  |  |  |  |  |
| W                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     | 7    |      |      |  |  |  |  |  |  |  |
| X                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| Y                         |      |      |     |     | 1   |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| Z                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| -                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| unknown (?)               |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| not sequenced             | 1    |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |  |  |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 6    | 7    | 7   | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7    | 7    | 7    |  |  |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 6    | 7    | 6   | 3   | 6   | 7    | 6   | 6   | 6   | 6   | 3    | 4   | 4   | 5   | 3   | 7    | 4   | 7    | 7    | 7    |  |  |  |  |  |  |  |
| mcaa <sup>4</sup>         | T    | C    | T   | F   | S   | G    | F   | S   | L   | S   | T    | S   | G   | M   | G   | V    | S   | W    | I    | R    |  |  |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 86% | 43% | 86% | 100% | 86% | 86% | 86% | 86% | 43%  | 57% | 57% | 71% | 43% | 100% | 57% | 100% | 100% | 100% |  |  |  |  |  |  |  |
| pos occupied <sup>6</sup> | 1    | 1    | 2   | 3   | 2   | 1    | 2   | 2   | 2   | 2   | 3    | 4   | 3   | 2   | 4   | 1    | 2   | 1    | 1    | 1    |  |  |  |  |  |  |  |

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Table 6C: Analysis of V heavy chain subgroup 2

| Framework I               |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
|---------------------------|-----|-----|------|------|-----|------|-----|------|------|-----|------|------|------|------|-----|-----|-----|------|------|------|
| amino acid <sup>1</sup>   | 1   | 2   | 3    | 4    | 5   | 6    | 7   | 8    | 9    | 10  | 11   | 12   | 13   | 14   | 15  | 16  | 17  | 18   | 19   | 20   |
| A                         |     |     |      |      |     |      |     |      |      | 3   |      |      |      |      |     |     |     |      |      |      |
| B                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| C                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| D                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| E                         | 1   |     |      |      |     | 6    |     |      |      |     |      |      |      |      |     | 2   |     |      |      |      |
| F                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| G                         |     |     |      |      |     |      |     | 6    |      |     |      |      |      |      |     |     |     |      |      |      |
| H                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| I                         |     | 1   |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| K                         |     |     |      |      | 3   |      |     |      |      |     |      |      | 6    |      | 1   |     |     |      |      |      |
| L                         |     |     |      | 6    |     |      |     |      |      |     | 6    |      |      |      |     |     |     | 6    |      | 6    |
| M                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| N                         |     |     |      |      |     |      | 1   |      |      |     |      |      |      |      |     |     |     |      |      |      |
| P                         |     |     |      |      |     |      | 1   |      | 6    |     |      |      |      | 6    |     |     | 1   |      |      |      |
| Q                         | 2   |     |      |      |     |      |     |      |      |     |      |      |      |      |     | 4   |     |      |      |      |
| R                         |     |     |      |      | 2   |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| S                         |     |     |      |      |     |      | 4   |      |      |     |      |      |      |      |     |     |     |      |      |      |
| T                         |     |     | 6    |      | 1   |      |     |      |      | 2   |      |      |      |      | 5   |     | 5   |      | 6    |      |
| V                         |     | 5   |      |      |     |      |     |      |      | 1   |      | 6    |      |      |     |     |     |      |      |      |
| W                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| X                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| Y                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| Z                         | 3   |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| -                         |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| unknown (?)               |     |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| not sequenced             | 1   | 1   | 1    | 1    | 1   | 1    | 1   | 1    | 1    | 1   | 1    | 1    | 1    | 1    | 1   | 1   | 1   | 1    | 1    | 1    |
| sum of seq <sup>2</sup>   | 6   | 6   | 6    | 6    | 6   | 6    | 6   | 6    | 6    | 6   | 6    | 6    | 6    | 6    | 6   | 6   | 6   | 6    | 6    | 6    |
| oomcaa <sup>3</sup>       | 3   | 5   | 6    | 6    | 3   | 6    | 4   | 6    | 6    | 3   | 6    | 6    | 6    | 6    | 5   | 4   | 5   | 6    | 6    | 6    |
| mcaa <sup>4</sup>         | Z   | V   | T    | L    | K   | E    | S   | G    | P    | A   | L    | V    | K    | P    | T   | Q   | T   | L    | T    | L    |
| rel. oomcaa <sup>5</sup>  | 50% | 83% | 100% | 100% | 50% | 100% | 67% | 100% | 100% | 50% | 100% | 100% | 100% | 100% | 83% | 67% | 83% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 3   | 2   | 1    | 1    | 3   | 1    | 3   | 1    | 1    | 3   | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 1    | 1    | 1    |

Table 6B: Analysis of V heavy chain subgroup 1B

| Framework IV              |     |      |      |     |      |      |     |      |     |     |     |      |     |
|---------------------------|-----|------|------|-----|------|------|-----|------|-----|-----|-----|------|-----|
| amino acid <sup>1</sup>   | 102 | 103  | 104  | 105 | 106  | 107  | 108 | 109  | 110 | 111 | 112 | 113  | sum |
| A                         |     |      |      |     |      |      |     |      |     |     |     |      | 340 |
| B                         |     |      |      |     |      |      |     |      |     |     |     |      |     |
| C                         |     |      |      |     |      |      |     |      |     |     |     |      | 79  |
| D                         | 2   |      |      |     |      |      |     |      |     |     |     |      | 179 |
| E                         |     |      |      | 1   |      |      |     |      |     |     |     |      | 159 |
| F                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 130 |
| G                         |     |      | 27   |     | 26   |      |     |      |     | 1   |     |      | 450 |
| H                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 51  |
| I                         | 7   |      |      |     |      |      |     |      | 3   |     |     |      | 113 |
| K                         |     |      |      | 2   |      |      |     |      |     |     |     |      | 194 |
| L                         |     |      |      |     |      |      | 12  |      |     | 1   |     |      | 204 |
| M                         |     |      |      |     |      |      | 2   |      |     |     |     |      | 144 |
| N                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 138 |
| P                         | 1   |      |      | 1   |      |      |     |      |     |     |     |      | 128 |
| Q                         |     |      |      | 23  |      |      |     |      |     |     |     |      | 253 |
| R                         |     |      |      |     |      |      | 1   |      |     |     |     |      | 247 |
| S                         | 3   |      |      |     |      |      |     |      | 1   |     | 18  | 18   | 432 |
| T                         |     |      |      |     |      | 21   | 6   |      | 16  |     | 1   |      | 390 |
| V                         | 6   |      |      |     |      |      |     | 21   |     | 18  |     |      | 342 |
| W                         |     | 29   |      |     |      |      |     |      |     |     |     |      | 158 |
| X                         |     |      |      |     |      |      |     |      |     |     |     |      |     |
| Y                         | 11  |      |      |     |      |      |     |      |     |     |     |      | 294 |
| Z                         |     |      |      |     |      |      |     |      |     |     |     |      |     |
| -                         | 3   |      |      |     |      |      |     |      |     |     |     |      | 394 |
| unknown (?)               |     |      |      |     |      |      |     |      |     |     |     |      | 3   |
| not sequenced             | 4   | 11   | 13   | 13  | 14   | 19   | 19  | 19   | 20  | 20  | 21  | 22   | 458 |
| sum of seq <sup>2</sup>   | 36  | 29   | 27   | 27  | 26   | 21   | 21  | 21   | 20  | 20  | 19  | 18   |     |
| oomcaa <sup>3</sup>       | 11  | 29   | 27   | 23  | 26   | 21   | 12  | 21   | 16  | 18  | 18  | 18   |     |
| mcaa <sup>4</sup>         | Y   | W    | G    | Q   | G    | T    | L   | V    | T   | V   | S   | S    |     |
| rel. oomcaa <sup>5</sup>  | 31% | 100% | 100% | 85% | 100% | 100% | 57% | 100% | 80% | 90% | 95% | 100% |     |
| pos occupied <sup>6</sup> | 10  | 1    | 1    | 4   | 1    | 1    | 4   | 1    | 3   | 3   | 2   | 1    |     |

Table 6B: Analysis of V heavy chain subgroup 1B

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |
| A                         | 37      | 1   | 6   |     | 1   | 1   |     | 2   | 3   | 1   | 3   |     | 1   |     |     |     |     | 5   |     |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |         | 1   |     |     |     | 3   |     |     |     | 2   | 1   |     |     |     |     |     |     |     |     |
| D                         |         |     | 7   |     | 5   | 2   | 3   | 1   | 5   | 4   |     | 1   |     | 2   | 2   | 1   | 2   |     | 27  |
| E                         |         |     | 2   |     | 1   |     |     | 1   | 1   |     | 2   |     | 1   |     | 1   |     |     |     |     |
| F                         |         |     |     | 1   | 1   | 3   |     |     | 2   | 1   | 1   | 1   | 1   |     |     |     |     | 2   | 15  |
| G                         |         | 1   | 7   | 7   | 5   | 5   | 9   | 4   | 7   | 1   | 3   |     | 2   | 2   | 1   |     | 1   | 3   | 1   |
| H                         |         |     | 1   |     |     |     | 2   |     |     | 1   | 1   |     |     |     |     |     |     |     |     |
| I                         |         | 1   |     | 1   | 1   | 3   | 1   | 1   | 1   | 1   | 1   | 1   |     |     |     |     |     |     | 1   |
| K                         |         | 1   |     |     | 1   |     |     |     | 1   | 1   |     | 1   |     | 1   |     |     | 1   |     |     |
| L                         |         |     | 2   | 4   | 4   | 4   | 3   |     |     | 1   | 2   | 1   | 1   | 2   |     | 1   |     |     | 2   |
| M                         |         |     |     | 2   |     | 1   | 1   |     |     |     |     |     |     |     | 1   |     |     |     | 4   |
| N                         |         |     |     |     | 1   |     |     | 1   |     | 1   | 1   | 1   |     |     | 3   |     | 1   |     | 1   |
| P                         |         |     |     | 6   | 4   |     |     |     | 1   | 1   |     | 3   | 2   |     |     |     | 1   |     |     |
| Q                         |         |     |     |     | 1   |     |     |     |     |     |     | 1   | 2   | 1   |     |     |     |     |     |
| R                         | 1       | 31  |     | 5   | 1   | 1   | 3   |     |     |     |     | 1   |     | 1   |     |     |     | 1   |     |
| S                         |         | 1   | 3   | 3   | 1   | 4   | 3   | 6   | 3   | 2   | 2   | 1   |     | 1   |     |     |     |     |     |
| T                         |         | 2   | 1   | 1   | 2   | 2   | 1   | 5   | 1   | 1   | 1   |     | 1   |     |     | 1   |     | 1   |     |
| V                         | 1       |     | 7   | 1   | 1   |     | 1   | 3   | 1   | 2   |     | 1   |     |     | 1   | 2   | 1   |     | 1   |
| W                         |         |     | 1   |     | 1   |     | 2   | 2   |     | 1   | 1   |     |     |     |     | 1   |     | 4   |     |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |         |     |     | 5   | 5   | 4   | 2   | 3   |     | 4   | 3   | 3   | 2   | 1   | 2   | 5   | 6   | 2   |     |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |         |     |     | 1   | 1   | 4   | 6   | 8   | 10  | 11  | 14  | 20  | 23  | 25  | 25  | 25  | 23  | 18  | 11  |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 3   |
| not sequenced             | 1       | 1   | 3   | 3   | 3   | 3   | 3   | 3   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| sum of seq <sup>2</sup>   | 39      | 39  | 37  | 37  | 37  | 37  | 37  | 37  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  |
| oomcaa <sup>3</sup>       | 37      | 31  | 7   | 7   | 5   | 5   | 9   | 8   | 10  | 11  | 14  | 20  | 23  | 25  | 25  | 25  | 23  | 18  | 15  |
| mcaa <sup>4</sup>         | A       | R   | D   | G   | D   | G   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   |
| rel. oomcaa <sup>5</sup>  | 95%     | 79% | 19% | 19% | 14% | 14% | 24% | 22% | 28% | 31% | 39% | 56% | 64% | 69% | 69% | 69% | 64% | 50% | 42% |
| pos occupied <sup>6</sup> | 3       | 8   | 10  | 12  | 18  | 13  | 13  | 12  | 12  | 17  | 14  | 13  | 10  | 9   | 8   | 7   | 8   | 8   | 5   |



Table 6B: Analysis of V heavy chain subgroup 1B

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|
|                           | 76            | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C   | 83  | 84  | 85  | 86   | 87   | 88   | 89  |
| A                         |               |     | 35  |     |     |     |     |     |     |     |     | 1   | 2   |      |      | 40   |     |
| B                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| C                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 37  |
| D                         | 1             |     |     |     |     | 4   |     |     |     |     |     | 19  | 40  |      |      | 1    |     |
| E                         |               |     |     |     |     | 35  |     |     |     |     |     | 19  |     |      |      |      |     |
| F                         |               |     | 1   |     |     |     |     |     |     |     |     | 2   |     |      |      |      | 2   |
| G                         |               |     |     |     |     | 1   |     | 1   | 2   |     |     |     |     |      |      |      | 1   |
| H                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| I                         |               | 1   |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 1   |
| K                         |               |     |     |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     |
| L                         |               |     |     |     | 2   | 39  |     |     |     | 39  |     |     |     |      |      | 2    | 1   |
| M                         |               |     |     |     | 37  | 1   |     |     |     |     |     |     |     |      |      | 2    |     |
| N                         | 7             |     |     |     |     |     |     | 1   | 2   |     |     |     |     |      |      |      |     |
| P                         |               |     |     |     |     |     |     |     |     |     |     | 1   |     |      |      |      | 1   |
| Q                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| R                         | 4             |     |     |     |     |     |     | 2   | 16  | 37  |     |     |     |      |      |      |     |
| S                         | 27            |     |     | 1   |     |     | 35  | 20  |     | 1   | 36  |     |     |      |      |      | 1   |
| T                         | 1             | 39  |     |     |     |     |     | 1   |     |     | 1   |     |     |      | 40   |      |     |
| V                         |               |     | 4   |     | 1   |     |     |     |     | 1   |     |     |     |      |      | 33   |     |
| W                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| X                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| Y                         |               |     |     | 39  |     |     |     |     |     |     |     |     |     |      |      |      | 38  |
| Z                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 35  |
| -                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| unknown (?)               |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |
| not sequenced             |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 1   |
| sum of seq <sup>2</sup>   | 40            | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40   | 40   | 39  |
| oomcaa <sup>3</sup>       | 27            | 39  | 35  | 39  | 37  | 35  | 39  | 35  | 20  | 39  | 37  | 36  | 19  | 40   | 40   | 40   | 33  |
| mcaa <sup>4</sup>         | S             | T   | A   | Y   | M   | E   | L   | S   | S   | L   | R   | S   | D   | D    | T    | A    | V   |
| rel. oomcaa <sup>5</sup>  | 68%           | 98% | 88% | 98% | 93% | 88% | 98% | 88% | 50% | 98% | 93% | 90% | 48% | 100% | 100% | 100% | 85% |
| pos occupied <sup>6</sup> | 5             | 2   | 3   | 2   | 3   | 3   | 2   | 5   | 4   | 2   | 4   | 4   | 3   | 1    | 1    | 1    | 5   |

Table 6B: Analysis of V heavy chain subgroup 1B

| CDR II                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|--|--|--|--|--|
| amino acid <sup>1</sup>   | 56  | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70   | 71  | 72  | 73  | 74  | 75  |  |  |  |  |  |
| A                         | 1   | 2   |     |     | 27  | 2   |     |     |     | 1   |     | 1   |     |     |      | 2   |     |     |     | 12  |  |  |  |  |  |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| C                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| D                         | 1   |     |     |     |     |     |     |     |     | 4   |     |     |     |     |      |     | 35  |     |     |     |  |  |  |  |  |
| E                         | 2   |     | 2   |     |     | 1   |     |     |     | 1   |     |     |     |     |      | 1   |     |     |     |     |  |  |  |  |  |
| F                         |     |     |     | 4   |     |     |     | 39  |     |     |     |     |     | 3   |      |     |     |     |     |     |  |  |  |  |  |
| G                         | 15  |     | 6   |     | 1   |     |     |     |     | 34  |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| H                         |     |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     |      |     | 1   |     |     |     |  |  |  |  |  |
| I                         |     | 1   | 1   |     |     |     |     |     |     |     |     | 1   | 1   | 13  |      |     |     |     |     | 22  |  |  |  |  |  |
| K                         | 2   | 2   | 8   |     |     |     | 36  |     | 1   |     |     |     |     |     |      | 1   |     |     |     |     |  |  |  |  |  |
| L                         |     |     |     |     |     | 1   |     | 1   |     |     |     |     |     | 1   |      |     |     |     |     |     |  |  |  |  |  |
| M                         |     |     |     |     |     |     |     |     |     |     |     |     |     | 23  |      |     |     | 1   |     | 1   |  |  |  |  |  |
| N                         | 17  |     | 18  |     |     |     | 1   |     |     |     |     |     |     |     |      |     | 4   |     |     |     |  |  |  |  |  |
| P                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     | 3   |     |  |  |  |  |  |
| Q                         |     |     |     |     |     | 36  |     |     | 37  |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| R                         |     |     | 2   |     |     |     | 1   |     | 2   | 37  |     |     |     |     |      | 34  |     | 1   |     |     |  |  |  |  |  |
| S                         | 1   |     |     | 2   | 11  |     | 1   |     |     |     |     |     |     |     |      | 1   |     |     | 37  |     |  |  |  |  |  |
| T                         |     | 35  | 2   |     | 1   |     | 1   |     |     |     |     |     | 39  |     | 40   | 1   |     | 38  |     | 5   |  |  |  |  |  |
| V                         | 1   |     |     |     |     |     |     |     |     |     |     | 38  |     |     |      |     |     |     |     |     |  |  |  |  |  |
| W                         |     |     |     |     |     |     |     |     |     |     | 3   |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| Y                         |     |     |     | 33  |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| -                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| not sequenced             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40  | 40  | 40  | 40  | 40  |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 17  | 35  | 18  | 33  | 27  | 36  | 36  | 39  | 37  | 34  | 37  | 38  | 39  | 23  | 40   | 34  | 35  | 38  | 37  | 22  |  |  |  |  |  |
| mcaa <sup>4</sup>         | N   | T   | N   | Y   | A   | Q   | K   | F   | Q   | G   | R   | V   | T   | M   | T    | R   | D   | T   | S   | I   |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 43% | 88% | 45% | 83% | 68% | 90% | 90% | 98% | 93% | 85% | 93% | 95% | 98% | 58% | 100% | 85% | 88% | 95% | 93% | 55% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 8   | 4   | 8   | 4   | 4   | 4   | 5   | 2   | 3   | 4   | 2   | 3   | 2   | 4   | 1    | 6   | 3   | 3   | 2   | 4   |  |  |  |  |  |

Table 6B: Analysis of V heavy chain subgroup 1B

|                           | Framework II |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41  | 42  | 43  | 44  | 45  | 46  | 47   | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              | 39  |     |     |     | 1   |     |     |      |     | 1   |     |     |     | 7   |      |      | 1   |     |     |  |  |  |  |
| B                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| C                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| D                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 1   |     |      |      |     | 1   |     |  |  |  |  |
| E                         |              |     |     | 1   |     |     | 39  |     |      |     |     |     |     |     |     |      |      | 1   | 1   |     |  |  |  |  |
| F                         |              |     |     |     |     |     | 2   |     |      |     |     |     | 1   |     |     |      |      | 1   |     |     |  |  |  |  |
| G                         |              |     |     | 39  |     | 28  |     |     |      |     | 39  | 1   |     |     | 1   |      |      | 9   | 1   | 39  |  |  |  |  |
| H                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      | 2   |     |     |  |  |  |  |
| I                         |              |     |     |     |     |     |     |     |      | 3   |     |     | 34  |     |     |      |      |     |     |     |  |  |  |  |
| K                         |              |     |     |     | 1   |     |     |     |      |     |     |     |     |     |     |      |      |     | 1   |     |  |  |  |  |
| L                         |              |     | 1   |     |     |     | 37  |     |      |     |     |     |     | 1   |     |      |      |     |     |     |  |  |  |  |
| M                         |              |     |     |     |     |     |     |     | 37   |     | 2   | 4   |     |     |     |      |      |     |     |     |  |  |  |  |
| N                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 35  |     |      |      | 20  | 12  | 1   |  |  |  |  |
| P                         |              | 1   | 34  |     |     |     | 1   |     |      |     |     |     |     |     | 31  |      |      |     |     |     |  |  |  |  |
| Q                         | 39           |     |     |     | 39  |     |     | 1   |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| R                         | 1            |     |     |     |     | 10  |     |     |      |     |     | 4   |     |     |     |      |      | 3   | 1   |     |  |  |  |  |
| S                         |              |     | 1   |     |     | 1   |     |     |      |     |     |     |     | 2   |     |      |      | 1   | 20  |     |  |  |  |  |
| T                         |              |     | 4   |     |     |     |     |     |      |     |     |     |     | 1   |     |      |      |     | 3   |     |  |  |  |  |
| V                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 1   | 1   |      |      |     |     |     |  |  |  |  |
| W                         |              |     |     |     |     |     |     |     | 40   |     |     | 33  |     |     |     |      |      |     |     |     |  |  |  |  |
| X                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| Y                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      | 2   |     |     |  |  |  |  |
| Z                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| -                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 40   | 40   |     |     |     |  |  |  |  |
| unknown (?)               |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| not sequenced             |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 40           | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40   | 40  | 40  | 40  |  |  |  |  |
| oomcaa <sup>3</sup>       | 39           | 39  | 34  | 39  | 39  | 28  | 37  | 39  | 40   | 37  | 39  | 33  | 34  | 35  | 31  | 40   | 40   | 20  | 20  | 39  |  |  |  |  |
| mcaa <sup>4</sup>         | Q            | A   | P   | G   | Q   | G   | L   | E   | W    | M   | G   | W   | I   | N   | P   | -    | -    | N   | S   | G   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 98%          | 98% | 85% | 98% | 98% | 70% | 93% | 98% | 100% | 93% | 98% | 83% | 85% | 88% | 78% | 100% | 100% | 50% | 50% | 98% |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 2   | 4   | 2   | 2   | 4   | 3   | 2   | 1    | 2   | 2   | 4   | 4   | 5   | 4   | 1    | 1    | 9   | 8   | 2   |  |  |  |  |

Table 6B: Analysis of V heavy chain subgroup 1B

|                           |      |      |     |     |      |      |     |     |     |     | CDRI |      |      |     |     |     |     |      |     |     |
|---------------------------|------|------|-----|-----|------|------|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|------|-----|-----|
| amino acid <sup>1</sup>   | 21   | 22   | 23  | 24  | 25   | 26   | 27  | 28  | 29  | 30  | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38  |
| A                         |      |      |     | 30  |      |      |     |     |     |     | 2    |      |      |     | 6   |     |     |      |     |     |
| B                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| C                         |      | 35   |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| D                         |      |      |     |     |      |      |     |     |     |     | 1    |      |      |     | 5   |     | 1   |      |     | 1   |
| E                         |      |      | 3   |     |      |      |     |     |     |     | 1    |      |      |     |     |     |     |      |     |     |
| F                         |      |      |     |     |      |      | 2   | 39  |     |     |      |      |      | 2   | 2   |     |     |      |     |     |
| G                         |      |      |     | 1   | 40   |      |     |     |     | 1   | 14   |      |      |     | 1   |     |     |      |     | 1   |
| H                         |      |      |     |     |      |      |     |     |     |     |      |      |      | 3   | 1   |     | 34  |      |     |     |
| I                         |      |      |     |     |      |      |     | 1   |     | 1   |      |      |      |     |     | 9   |     |      |     |     |
| K                         |      |      | 28  |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| L                         |      |      |     |     |      |      |     |     | 1   |     | 1    |      |      |     |     | 5   |     |      | 2   |     |
| M                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     | 23  |     |      |     |     |
| N                         |      |      |     |     |      |      | 1   |     |     | 1   | 3    |      |      |     |     | 1   | 3   |      |     |     |
| P                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     | 1   |     |     |      |     |     |
| Q                         |      |      | 2   |     |      |      |     |     |     |     | 1    |      |      |     | 1   |     | 1   |      |     | 1   |
| R                         |      |      | 2   |     |      |      |     | 2   |     |     |      |      |      | 1   |     |     |     |      |     | 37  |
| S                         | 35   |      |     |     | 40   |      |     | 5   |     | 2   | 15   |      |      | 2   | 1   |     |     |      |     |     |
| T                         |      |      |     | 3   |      |      |     | 32  |     | 34  |      |      |      |     | 1   |     |     |      |     |     |
| V                         |      |      |     | 1   |      |      | 1   |     |     | 1   | 1    |      |      |     | 2   | 2   |     |      | 38  |     |
| W                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     | 40   |     |     |
| X                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| Y                         |      |      |     |     |      |      | 36  |     |     |     | 1    |      |      | 32  | 19  |     | 1   |      |     |     |
| Z                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| -                         |      |      |     |     |      |      |     |     |     |     |      | 40   | 40   |     |     |     |     |      |     |     |
| unknown (?)               |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| not sequenced             | 5    | 5    | 5   | 5   |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |
| sum of seq <sup>2</sup>   | 35   | 35   | 35  | 35  | 40   | 40   | 40  | 40  | 40  | 40  | 40   | 40   | 40   | 40  | 40  | 40  | 40  | 40   | 40  | 40  |
| oomcaa <sup>3</sup>       | 35   | 35   | 28  | 30  | 40   | 40   | 36  | 32  | 39  | 34  | 15   | 40   | 40   | 32  | 19  | 23  | 34  | 40   | 38  | 37  |
| mcaa <sup>4</sup>         | S    | C    | K   | A   | S    | G    | Y   | T   | F   | T   | S    | -    | -    | Y   | Y   | M   | H   | W    | V   | R   |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 80% | 86% | 100% | 100% | 90% | 80% | 98% | 85% | 38%  | 100% | 100% | 80% | 48% | 58% | 85% | 100% | 95% | 93% |
| pos occupied <sup>6</sup> | 1    | 1    | 4   | 4   | 1    | 1    | 4   | 4   | 2   | 6   | 10   | 1    | 1    | 5   | 11  | 5   | 5   | 1    | 2   | 4   |

Table 6B: Analysis of V heavy chain subgroup 1B

| Framework I               |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|------|------|-----|------|------|-----|-----|-----|------|-----|-----|------|-----|-----|
| amino acid <sup>1</sup>   | 1   | 2   | 3   | 4   | 5   | 6   | 7    | 8    | 9   | 10   | 11   | 12  | 13  | 14  | 15   | 16  | 17  | 18   | 19  | 20  |
| A                         |     |     |     |     |     |     |      |      | 32  |      |      |     |     |     |      | 34  |     |      |     |     |
| B                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| C                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| D                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| E                         |     | 1   |     |     | 5   | 1   |      |      |     | 35   |      |     |     |     |      |     |     |      |     |     |
| F                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| G                         |     |     |     |     |     |     |      | 27   |     |      |      |     |     |     | 35   |     |     |      |     |     |
| H                         |     |     | 1   |     |     |     |      |      |     |      |      |     |     | 1   |      |     |     |      |     |     |
| I                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     | 1   |
| K                         |     | 3   | 1   |     |     |     |      |      |     |      |      | 34  | 33  |     |      |     |     |      | 33  |     |
| L                         |     |     | 3   | 26  | 1   |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| M                         |     |     |     | 1   | 1   |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| N                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| P                         |     |     |     |     |     |     |      |      | 1   |      |      |     |     | 33  |      |     | 1   |      |     |     |
| Q                         | 21  |     | 20  |     |     | 26  |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| R                         | 1   |     |     |     |     |     |      |      |     |      |      | 1   | 2   |     |      |     |     |      |     |     |
| S                         |     |     |     |     |     |     | 27   |      |     |      |      |     |     |     |      | 1   | 34  |      |     |     |
| T                         |     |     |     |     |     |     |      |      | 1   |      |      |     |     | 1   |      |     |     |      | 2   |     |
| V                         | 3   | 21  |     |     | 20  |     |      |      |     | 35   |      |     |     |     |      |     |     | 35   |     | 34  |
| W                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| X                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| Y                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| Z                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| -                         |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| unknown (?)               |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| not sequenced             | 15  | 15  | 15  | 13  | 13  | 13  | 13   | 13   | 6   | 5    | 5    | 5   | 5   | 5   | 5    | 5   | 5   | 5    | 5   | 5   |
| sum of seq <sup>2</sup>   | 25  | 25  | 25  | 27  | 27  | 27  | 27   | 27   | 34  | 35   | 35   | 35  | 35  | 35  | 35   | 35  | 35  | 35   | 35  | 35  |
| oomcaa <sup>3</sup>       | 21  | 21  | 20  | 26  | 20  | 26  | 27   | 27   | 32  | 35   | 35   | 34  | 33  | 33  | 35   | 34  | 34  | 35   | 33  | 34  |
| mcaa <sup>4</sup>         | Q   | V   | Q   | L   | V   | Q   | S    | G    | A   | E    | V    | K   | K   | P   | G    | A   | S   | V    | K   | V   |
| rel. oomcaa <sup>5</sup>  | 84% | 84% | 80% | 96% | 74% | 96% | 100% | 100% | 94% | 100% | 100% | 97% | 94% | 94% | 100% | 97% | 97% | 100% | 94% | 97% |
| pos occupied <sup>6</sup> | 3   | 3   | 4   | 2   | 4   | 2   | 1    | 1    | 3   | 1    | 1    | 2   | 2   | 3   | 1    | 2   | 2   | 1    | 2   | 2   |

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Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>   | Framework IV |     |     |     |      |     |     |     |     |      |     |     | sum |
|---------------------------|--------------|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
|                           | 102          | 103 | 104 | 105 | 106  | 107 | 108 | 109 | 110 | 111  | 112 | 113 |     |
| A                         |              |     |     |     |      |     |     |     |     |      |     |     | 670 |
| B                         |              |     |     |     |      |     |     |     |     |      |     |     |     |
| C                         |              |     |     |     |      |     |     |     |     |      |     |     | 165 |
| D                         |              | 1   | 1   |     |      |     |     |     |     |      |     |     | 308 |
| E                         | 1            | 1   |     |     |      |     |     |     |     |      |     |     | 297 |
| F                         | 2            |     |     |     |      |     |     |     |     |      |     |     | 226 |
| G                         |              |     | 58  |     | 59   | 1   | 1   |     |     |      |     |     | 928 |
| H                         |              |     |     | 1   |      |     |     |     |     |      |     |     | 14  |
| I                         | 3            |     |     |     |      |     |     |     | 4   |      |     |     | 286 |
| K                         |              |     |     | 3   |      | 1   |     |     |     |      |     |     | 325 |
| L                         | 3            |     |     | 1   |      |     | 40  | 1   |     |      |     |     | 386 |
| M                         | 1            |     |     |     |      |     | 3   |     |     |      |     |     | 189 |
| N                         |              |     |     | 1   |      |     |     |     |     |      |     |     | 176 |
| P                         | 5            |     |     |     |      |     |     |     |     |      |     | 1   | 238 |
| Q                         |              |     |     | 52  |      |     |     |     |     |      |     |     | 494 |
| R                         |              |     |     | 1   |      |     |     |     |     |      |     |     | 351 |
| S                         |              |     |     |     |      |     |     |     |     |      | 53  | 51  | 972 |
| T                         |              |     |     |     |      | 54  | 11  | 1   | 51  |      | 1   |     | 736 |
| V                         | 15           |     | 1   |     |      |     | 1   | 54  |     | 54   |     | 1   | 699 |
| W                         |              | 59  |     | 1   |      |     |     |     |     |      |     |     | 243 |
| X                         |              |     |     |     |      |     |     |     |     |      |     |     |     |
| Y                         | 34           |     | 1   |     |      |     |     |     |     |      |     |     | 542 |
| Z                         |              |     |     |     |      |     |     |     |     |      |     |     | 3   |
| -                         | 1            |     |     |     |      |     |     |     |     |      |     |     | 578 |
| unknown (?)               |              |     |     |     |      |     |     |     |     |      |     |     | 8   |
| not sequenced             | 5            | 9   | 9   | 10  | 11   | 14  | 14  | 14  | 15  | 16   | 16  | 17  | 406 |
| sum of seq <sup>7</sup>   | 65           | 61  | 61  | 60  | 59   | 56  | 56  | 56  | 55  | 54   | 54  | 53  |     |
| oomcaa <sup>3</sup>       | 34           | 59  | 58  | 52  | 59   | 54  | 40  | 54  | 51  | 54   | 53  | 51  |     |
| mcaa <sup>4</sup>         | Y            | W   | G   | Q   | G    | T   | L   | V   | T   | V    | S   | S   |     |
| rel. oomcaa <sup>5</sup>  | 52%          | 97% | 95% | 87% | 100% | 96% | 71% | 96% | 93% | 100% | 98% | 96% |     |
| pos occupied <sup>6</sup> | 9            | 3   | 4   | 7   | 1    | 3   | 5   | 3   | 2   | 1    | 2   | 3   |     |

Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>    | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                            | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   |
| A                          | 66      | 2   | 16  |     | 1   | 1   | 1   | 4   | 1   | 2   | 2   | 1   | 1   |     | 1   | 1   | 2   |
| B                          |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                          |         |     |     |     | 1   | 1   | 16  | 2   |     | 1   | 1   | 7   | 2   | 1   |     |     |     |
| D                          |         |     | 16  | 5   | 3   |     | 3   | 5   | 4   | 3   | 4   |     |     | 1   | 1   | 14  | 59  |
| E                          |         |     | 9   |     |     |     | 2   |     |     | 1   |     |     | 1   |     |     | 1   |     |
| F                          |         |     |     |     | 1   | 3   |     | 2   |     | 3   | 1   | 2   |     | 2   | 1   |     | 28  |
| G                          |         | 2   | 14  | 13  | 20  | 10  | 14  | 5   | 20  | 15  | 16  | 3   | 3   | 4   | 15  | 1   | 7   |
| H                          |         |     |     |     |     |     |     |     |     | 1   | 1   | 1   |     | 1   |     |     |     |
| I                          |         |     |     | 2   | 5   | 2   | 2   |     | 2   | 2   | 1   | 1   |     |     | 1   |     |     |
| K                          |         | 5   |     |     | 2   | 1   |     |     | 1   |     |     |     |     |     |     |     |     |
| L                          |         | 1   | 4   | 4   | 2   | 5   | 2   | 1   | 1   |     | 4   | 2   |     | 1   |     | 1   | 1   |
| M                          |         |     | 1   |     | 2   |     | 1   |     | 1   |     |     | 1   | 1   |     |     |     | 10  |
| N                          |         |     |     | 2   | 2   | 1   | 2   | 1   | 2   | 2   | 2   | 2   |     |     | 1   | 1   | 4   |
| P                          |         |     |     | 20  | 3   |     | 1   | 3   | 2   | 2   | 2   | 4   | 2   | 1   | 4   | 1   | 1   |
| Q                          |         |     |     | 1   |     |     | 1   |     | 1   | 1   | 1   |     |     |     |     |     |     |
| R                          |         | 55  | 1   | 5   | 7   | 8   | 1   | 4   |     | 2   |     | 1   |     | 16  |     |     |     |
| S                          |         | 1   | 1   | 5   | 5   | 5   | 5   | 21  | 5   | 11  | 8   | 4   | 3   |     | 2   | 1   | 2   |
| T                          | 1       | 3   | 3   | 5   | 4   | 1   | 3   | 4   | 2   | 5   | 2   |     | 1   |     |     | 1   | 1   |
| V                          | 3       |     | 3   | 2   | 4   | 3   | 3   | 3   | 4   | 2   | 2   | 2   | 1   | 2   | 1   |     |     |
| W                          |         |     |     | 1   | 1   | 3   | 1   | 1   |     |     | 2   |     | 3   |     |     | 1   | 5   |
| X                          |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                          |         | 1   |     | 2   | 3   | 20  | 5   | 4   | 9   | 1   | 2   | 11  | 20  | 10  | 6   | 9   | 10  |
| Z                          |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                          |         |     |     | 1   | 2   | 2   | 3   | 6   | 11  | 11  | 14  | 23  | 26  | 26  | 31  | 34  | 46  |
| unknown (?)                |         |     |     |     |     |     |     |     |     |     |     |     | 1   |     | 1   | 1   | 2   |
| not sequenced <sup>5</sup> |         |     | 2   | 2   | 2   | 4   | 4   | 4   | 4   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   |
| sum of seq <sup>2</sup>    | 70      | 70  | 68  | 68  | 68  | 66  | 66  | 66  | 66  | 65  | 65  | 65  | 65  | 65  | 65  | 65  | 65  |
| oomcaa <sup>3</sup>        | 66      | 55  | 16  | 20  | 20  | 20  | 16  | 21  | 20  | 15  | 16  | 23  | 26  | 26  | 31  | 34  | 46  |
| mcaa <sup>4</sup>          | A       | R   | A   | P   | G   | Y   | C   | S   | G   | -   | -   | -   | -   | -   | -   | -   | F   |
| rel. oomcaa <sup>5</sup>   | 94%     | 79% | 24% | 29% | 29% | 30% | 24% | 32% | 30% | 23% | 25% | 35% | 40% | 40% | 48% | 52% | 71% |
| pos occupied <sup>6</sup>  | 3       | 8   | 10  | 14  | 18  | 15  | 18  | 15  | 15  | 17  | 17  | 15  | 12  | 11  | 11  | 10  | 8   |

Table 6A: Analysis of V heavy chain subgroup 1A

| Framework III             |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|-----|------|-----|-----|-----|------|
| amino acid <sup>1</sup>   | 76  | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    | 83  | 84  | 85  | 86   | 87  | 88   | 89  | 90  | 91  | 92   |
| A                         |     |     | 64  |     |     | 1   |     |     |     |      |     | 3   |     |      | 1   | 70   |     |     |     |      |
| B                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| C                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     | 70   |
| D                         |     |     |     |     |     | 2   |     |     |     |      |     |     | 26  | 70   |     |      |     |     |     |      |
| E                         |     |     |     |     |     | 64  |     |     |     |      |     |     | 44  |      |     |      |     |     |     |      |
| F                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      | 1   | 1   | 2   |      |
| G                         |     |     |     |     |     |     |     |     | 1   |      |     |     |     |      |     |      |     |     |     |      |
| H                         |     |     |     | 1   |     |     |     | 1   |     |      |     |     |     |      |     |      |     |     |     |      |
| I                         |     | 1   |     |     |     |     | 3   | 1   | 1   |      |     |     |     |      |     |      | 2   |     |     |      |
| K                         |     |     |     |     |     |     |     |     |     |      |     | 3   |     |      |     |      |     |     |     |      |
| L                         |     |     |     |     | 3   |     | 63  |     |     | 70   |     |     |     |      |     |      | 2   |     |     |      |
| M                         |     |     |     |     | 67  |     |     |     |     |      |     |     |     |      | 1   |      | 1   |     |     |      |
| N                         | 4   |     |     |     |     |     |     | 1   | 16  |      |     |     |     |      |     |      |     |     |     |      |
| P                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| Q                         |     |     |     | 1   |     | 3   |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| R                         | 3   |     |     |     |     |     |     | 23  | 1   |      | 62  |     |     |      |     |      |     |     |     |      |
| S                         | 62  |     | 1   |     |     |     |     | 41  | 49  |      | 67  |     |     |      | 1   |      |     |     |     |      |
| T                         | 1   | 69  | 2   |     |     |     |     | 3   | 2   |      | 4   |     |     |      | 67  |      |     |     |     |      |
| V                         |     |     | 3   |     |     |     | 4   |     |     |      | 1   |     |     |      |     |      | 64  |     |     |      |
| W                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| X                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| Y                         |     |     |     | 68  |     |     |     |     |     |      |     |     |     |      |     |      |     | 69  | 68  |      |
| Z                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| -                         |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| unknown (?)               |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| not sequenced             |     |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| sum of seq <sup>2</sup>   | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70  | 70  | 70  | 70   | 70  | 70   | 70  | 70  | 70  | 70   |
| oomcaa <sup>1</sup>       | 62  | 69  | 64  | 68  | 67  | 64  | 63  | 41  | 49  | 70   | 62  | 67  | 44  | 70   | 67  | 70   | 64  | 69  | 68  | 70   |
| mcaa <sup>1</sup>         | S   | T   | A   | Y   | M   | E   | L   | S   | S   | L    | R   | S   | E   | D    | T   | A    | V   | Y   | Y   | C    |
| rel. oomcaa <sup>3</sup>  | 89% | 99% | 91% | 97% | 96% | 91% | 90% | 59% | 70% | 100% | 89% | 96% | 63% | 100% | 96% | 100% | 91% | 99% | 97% | 100% |
| pos occupied <sup>6</sup> | 4   | 2   | 4   | 3   | 2   | 4   | 3   | 6   | 6   | 1    | 4   | 2   | 2   | 1    | 4   | 1    | 5   | 2   | 2   | 1    |

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Table 6A: Analysis of V heavy chain subgroup 1A

|                           | CDR II |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
|---------------------------|--------|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|------|-----|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61   | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72   | 73  | 74   | 75  |  |
| A                         | 1      | 34  |     |     | 69  |      |     |     |     |     |     |     |     |     |     | 43  |      |     |      |     |  |
| B                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| C                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| D                         | 15     |     | 1   |     |     |      |     |     |     | 2   |     |     |     |     |     |     | 70   |     |      |     |  |
| E                         |        |     |     |     |     |      |     |     | 1   |     |     |     |     |     |     |     |      | 33  |      |     |  |
| F                         |        |     |     | 1   |     |      | 48  |     |     |     |     | 3   |     | 4   |     |     |      |     |      |     |  |
| G                         | 1      |     |     |     |     |      | 3   |     | 67  |     |     |     |     |     |     |     |      |     |      |     |  |
| H                         |        |     | 1   |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| I                         | 4      |     |     |     |     |      |     |     |     |     |     |     | 1   | 44  |     |     |      | 1   |      |     |  |
| K                         | 1      |     | 2   | 1   |     |      | 47  |     | 1   |     | 1   |     |     |     |     |     |      | 8   |      |     |  |
| L                         | 1      | 1   |     |     |     |      |     | 22  |     |     |     | 2   |     | 1   |     | 3   |      |     |      |     |  |
| M                         |        |     |     |     |     |      |     |     |     |     |     |     |     | 21  |     |     |      |     |      |     |  |
| N                         | 9      |     | 59  |     |     |      | 18  |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| P                         | 1      | 7   |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| Q                         | 1      | 1   |     |     |     | 70   |     |     | 64  |     |     |     |     |     |     |     |      |     |      |     |  |
| R                         | 2      |     |     |     |     |      | 2   |     | 1   |     | 69  |     |     |     |     |     |      | 1   |      |     |  |
| S                         |        | 1   | 2   |     | 1   |      |     |     |     |     |     |     |     |     | 5   |     |      |     | 70   |     |  |
| T                         | 34     | 26  | 4   |     |     |      |     |     | 3   |     |     |     | 66  |     | 65  | 24  |      | 27  |      | 67  |  |
| V                         |        |     |     |     |     |      |     |     |     | 1   |     | 65  | 3   |     |     |     |      |     |      | 3   |  |
| W                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| X                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| Y                         |        |     | 1   | 68  |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| Z                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| -                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| unknown (?)               |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| not sequenced             |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |  |
| sum of seq <sup>2</sup>   | 70     | 70  | 70  | 70  | 70  | 70   | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70  | 70   | 70  |  |
| oomcaa <sup>3</sup>       | 34     | 34  | 59  | 68  | 69  | 70   | 47  | 48  | 64  | 67  | 69  | 65  | 66  | 44  | 65  | 43  | 70   | 33  | 70   | 67  |  |
| mcaa <sup>4</sup>         | T      | A   | N   | Y   | A   | Q    | K   | F   | Q   | G   | R   | V   | T   | I   | T   | A   | D    | E   | S    | T   |  |
| rel. oomcaa <sup>5</sup>  | 49%    | 49% | 84% | 97% | 99% | 100% | 67% | 69% | 91% | 96% | 99% | 93% | 94% | 63% | 93% | 61% | 100% | 47% | 100% | 96% |  |
| pos occupied <sup>6</sup> | 11     | 6   | 7   | 3   | 2   | 1    | 4   | 2   | 5   | 3   | 2   | 3   | 3   | 4   | 2   | 3   | 1    | 5   | 1    | 2   |  |

Table 6A: Analysis of V heavy chain subgroup 1A

|                           | Framework II |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
|---------------------------|--------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40   | 41  | 42  | 43  | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              | 70   |     |     |     |     |     |     |     |     | 1   |     |     |     | 5   |      |      |     |     |     |  |  |  |  |
| B                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| C                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| D                         |              |      |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| E                         |              |      |     |     |     |     |     | 69  |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| F                         |              |      |     |     |     |     |     |     |     |     |     |     |     | 2   |     |      |      | 3   | 39  |     |  |  |  |  |
| G                         |              |      | 1   | 68  |     | 69  |     |     | 1   |     | 69  | 39  |     |     | 1   |      |      |     |     | 68  |  |  |  |  |
| H                         |              |      | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| I                         |              |      |     |     |     |     |     |     |     |     |     |     | 65  | 38  |     |      |      | 34  |     |     |  |  |  |  |
| K                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| L                         |              |      |     | 1   |     | 68  |     |     | 1   |     | 1   |     |     |     |     |      |      | 2   | 4   |     |  |  |  |  |
| M                         |              |      |     |     |     |     |     |     | 67  |     |     |     |     | 2   |     |      |      | 4   |     |     |  |  |  |  |
| N                         |              |      |     |     |     |     |     |     |     |     |     |     |     | 4   |     |      |      | 3   | 22  |     |  |  |  |  |
| P                         |              |      | 68  |     |     |     | 1   |     |     |     |     |     |     |     | 44  |      |      |     |     |     |  |  |  |  |
| Q                         | 69           |      |     |     | 69  |     |     |     |     |     |     |     |     |     |     |      |      | 1   | 1   | 1   |  |  |  |  |
| R                         | 1            |      |     | 1   |     | 1   |     |     |     |     |     | 4   |     |     |     |      |      | 1   |     |     |  |  |  |  |
| S                         |              |      |     |     | 1   |     |     |     | 1   | 1   |     |     |     | 22  |     |      |      |     | 1   | 1   |  |  |  |  |
| T                         |              |      |     |     |     |     |     |     |     |     |     |     | 1   | 2   | 4   |      |      | 1   | 3   |     |  |  |  |  |
| V                         |              |      |     |     |     |     |     |     |     | 1   |     |     | 2   | 2   | 16  |      |      | 1   |     |     |  |  |  |  |
| W                         |              |      |     |     |     |     | 1   | 67  |     |     |     | 26  |     |     |     |      |      |     |     |     |  |  |  |  |
| X                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| Y                         |              |      |     |     |     |     |     |     | 1   |     |     |     |     |     |     |      |      | 20  |     |     |  |  |  |  |
| Z                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| -                         |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     | 70   | 70   |     |     |     |  |  |  |  |
| unknown (?)               |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| not sequenced             |              |      |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| sum of seq <sup>1</sup>   | 70           | 70   | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70   | 70  | 70  | 70  |  |  |  |  |
| oomcaa <sup>1</sup>       | 69           | 70   | 68  | 68  | 69  | 69  | 68  | 69  | 67  | 67  | 69  | 39  | 65  | 38  | 44  | 70   | 70   | 34  | 39  | 68  |  |  |  |  |
| mcaa <sup>1</sup>         | Q            | A    | P   | G   | Q   | G   | L   | E   | W   | M   | G   | G   | I   | I   | P   | -    | -    | I   | F   | G   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 99%          | 100% | 97% | 97% | 99% | 99% | 97% | 99% | 96% | 96% | 99% | 56% | 93% | 54% | 63% | 100% | 100% | 49% | 56% | 97% |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 1    | 3   | 3   | 2   | 2   | 3   | 2   | 4   | 4   | 2   | 4   | 4   | 6   | 5   | 1    | 1    | 10  | 6   | 3   |  |  |  |  |

Table 6A: Analysis of V heavy chain subgroup 1A

|                           |     |     |     |     |      |      |     |     |     |     | CDRI |      |      |     |     |     |     |      |     |      |
|---------------------------|-----|-----|-----|-----|------|------|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|------|-----|------|
| amino acid <sup>1</sup>   | 21  | 22  | 23  | 24  | 25   | 26   | 27  | 28  | 29  | 30  | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38   |
| A                         |     |     |     | 62  |      |      |     | 1   |     |     |      |      |      |     | 41  |     |     |      |     |      |
| B                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| C                         |     | 63  |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| D                         |     |     |     |     |      |      | 1   |     |     |     |      |      |      |     |     |     |     |      |     |      |
| E                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| F                         |     |     |     |     |      |      |     |     | 69  |     |      |      |      |     | 3   |     | 3   |      |     |      |
| G                         |     |     |     | 1   |      | 69   | 41  |     | 1   |     |      |      |      |     | 23  |     |     |      |     |      |
| H                         |     |     |     |     |      |      |     |     |     | 1   |      |      |      |     | 1   |     |     | 1    |     |      |
| I                         |     |     |     |     |      |      |     | 1   |     |     |      |      |      |     |     | 61  | 1   |      | 1   |      |
| K                         |     |     | 63  |     |      |      |     |     |     | 1   | 1    |      |      |     |     |     |     |      |     |      |
| L                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     | 1   | 2   |     |      |     |      |
| M                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     | 4   |     |      |     |      |
| N                         |     |     |     |     |      |      |     |     |     | 2   | 5    |      |      |     |     |     | 4   |      |     |      |
| P                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     | 1   |     |     |      |     |      |
| Q                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| R                         |     | 1   | 1   |     |      |      |     |     |     | 1   | 1    |      |      |     |     |     |     |      |     | 70   |
| S                         | 63  |     |     |     | 68   |      | 1   |     |     | 40  | 60   |      |      | 2   |     |     | 60  |      |     |      |
| T                         | 1   |     |     | 2   |      |      |     | 68  |     | 25  | 3    |      |      |     | 3   |     | 4   |      |     |      |
| V                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     | 1   |     |     |      | 69  |      |
| W                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     | 70   |     |      |
| X                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| Y                         |     |     |     |     |      |      | 27  |     |     |     |      |      |      |     | 64  |     |     |      |     |      |
| Z                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| -                         |     |     |     |     |      |      |     |     |     |     |      | 70   | 70   |     |     |     |     |      |     |      |
| unknown (?)               |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| not sequenced             | 6   | 6   | 6   | 5   | 2    | 1    |     |     |     |     |      |      |      |     |     |     |     |      |     |      |
| sum of seq <sup>2</sup>   | 64  | 64  | 64  | 65  | 68   | 69   | 70  | 70  | 70  | 70  | 70   | 70   | 70   | 70  | 70  | 70  | 70  | 70   | 70  | 70   |
| oomcaa <sup>3</sup>       | 63  | 63  | 63  | 62  | 68   | 69   | 41  | 68  | 69  | 40  | 60   | 70   | 70   | 64  | 41  | 61  | 60  | 70   | 69  | 70   |
| mcaa <sup>4</sup>         | S   | C   | K   | A   | S    | G    | G   | T   | F   | S   | S    | -    | -    | Y   | A   | I   | S   | W    | V   | R    |
| rel. oomcaa <sup>5</sup>  | 98% | 98% | 98% | 95% | 100% | 100% | 59% | 97% | 99% | 57% | 86%  | 100% | 100% | 91% | 59% | 87% | 86% | 100% | 99% | 100% |
| pos occupied <sup>6</sup> | 2   | 2   | 2   | 3   | 1    | 1    | 4   | 3   | 2   | 6   | 5    | 1    | 1    | 4   | 6   | 4   | 5   | 1    | 2   | 1    |

Table 6A: Analysis of V heavy chain subgroup 1A

| Framework I               |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
|---------------------------|-----|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|------|-----|------|-----|-----|------|-----|------|
| amino acid <sup>1</sup>   | 1   | 2   | 3   | 4   | 5   | 6   | 7    | 8   | 9   | 10   | 11  | 12  | 13   | 14  | 15   | 16  | 17  | 18   | 19  | 20   |
| A                         |     |     |     |     | 1   | 14  |      |     | 60  |      |     |     |      |     |      | 24  | 1   |      |     |      |
| B                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| C                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| D                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| E                         | 1   |     |     |     | 2   | 1   |      | 2   |     | 64   |     |     |      |     |      |     |     |      |     |      |
| F                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| G                         |     |     |     |     |     |     |      | 58  | 1   |      |     |     |      |     |      | 64  |     |      |     |      |
| H                         |     |     | 2   |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| I                         |     | 2   |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| K                         |     | 2   |     |     |     |     |      |     |     |      |     | 57  | 64   |     |      |     |     |      | 60  |      |
| L                         |     |     | 2   | 59  |     |     |      |     |     |      | 3   |     |      |     |      |     |     |      |     |      |
| M                         |     | 1   |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| N                         |     |     |     |     |     |     |      |     |     |      |     | 6   |      |     |      |     |     |      |     |      |
| P                         |     |     |     |     |     |     |      |     |     |      |     |     |      | 63  |      |     |     |      |     |      |
| Q                         | 53  |     | 56  |     | 2   | 45  |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| R                         |     |     |     |     |     |     |      |     |     |      |     | 1   |      |     |      |     |     |      | 3   |      |
| S                         |     |     |     |     |     |     | 60   |     | 3   |      |     |     |      | 1   |      | 40  | 63  |      |     |      |
| T                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      | 1   |      |
| V                         | 2   | 55  |     | 1   | 55  |     |      |     |     | 61   |     |     |      |     |      |     |     | 64   |     | 64   |
| W                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| X                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| Y                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| Z                         | 3   |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| -                         |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| unknown (?)               |     |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| not sequenced             | 11  | 10  | 10  | 10  | 10  | 10  | 10   | 10  | 6   | 6    | 6   | 6   | 6    | 6   | 6    | 6   | 6   | 6    | 6   | 6    |
| sum of seq <sup>7</sup>   | 59  | 60  | 60  | 60  | 60  | 60  | 60   | 60  | 64  | 64   | 64  | 64  | 64   | 64  | 64   | 64  | 64  | 64   | 64  | 64   |
| oomcaa <sup>3</sup>       | 53  | 55  | 56  | 59  | 55  | 45  | 60   | 58  | 60  | 64   | 61  | 57  | 64   | 63  | 64   | 40  | 63  | 64   | 60  | 64   |
| mcaa <sup>4</sup>         | Q   | V   | Q   | L   | V   | Q   | S    | G   | A   | E    | V   | K   | K    | P   | G    | S   | S   | V    | K   | V    |
| rel. oomcaa <sup>5</sup>  | 90% | 92% | 93% | 98% | 92% | 75% | 100% | 97% | 94% | 100% | 95% | 89% | 100% | 98% | 100% | 63% | 98% | 100% | 94% | 100% |
| pos occupied <sup>6</sup> | 4   | 4   | 3   | 2   | 4   | 3   | 1    | 2   | 3   | 1    | 2   | 3   | 1    | 2   | 1    | 2   | 2   | 1    | 3   | 1    |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework IV |     |      |      |     |     |      |      |     |     |      | sum |
|---------------------------|--------------|-----|------|------|-----|-----|------|------|-----|-----|------|-----|
|                           | 99           | 100 | 101  | 102  | 103 | 104 | 105  | 106  | A   | 107 | 108  |     |
| A                         |              |     |      |      |     |     |      |      |     |     |      | 265 |
| B                         |              |     |      |      |     |     |      |      |     |     |      |     |
| C                         |              |     |      |      |     |     |      |      |     | 1   |      | 82  |
| D                         |              |     |      |      |     |     |      |      |     |     |      | 225 |
| E                         |              |     |      |      | 2   |     |      |      |     |     |      | 145 |
| F                         |              |     |      |      |     |     |      |      |     |     |      | 90  |
| G                         | 35           | 31  | 35   |      |     |     |      |      |     | 24  |      | 461 |
| H                         |              |     |      |      |     |     |      |      |     |     |      | 32  |
| I                         |              |     |      |      |     |     |      |      |     |     |      | 160 |
| K                         |              |     |      |      | 30  |     |      |      |     |     |      | 110 |
| L                         |              |     |      |      |     | 28  |      |      | 33  |     |      | 233 |
| M                         |              |     |      |      |     |     |      |      |     |     |      | 17  |
| N                         |              |     |      |      |     |     |      |      |     |     |      | 126 |
| P                         |              |     |      |      |     |     |      |      | 1   |     |      | 249 |
| Q                         |              |     |      |      |     |     |      |      |     |     | 7    | 275 |
| R                         |              |     |      |      | 2   |     |      |      |     |     |      | 154 |
| S                         |              |     |      |      |     |     |      |      |     | 2   |      | 501 |
| T                         |              | 4   |      | 35   |     |     | 35   |      |     |     |      | 347 |
| V                         |              |     |      |      |     | 7   |      | 35   |     |     |      | 308 |
| W                         |              |     |      |      |     |     |      |      |     |     |      | 62  |
| X                         |              |     |      |      |     |     |      |      |     |     |      |     |
| Y                         |              |     |      |      |     |     |      |      |     |     |      | 211 |
| Z                         |              |     |      |      |     |     |      |      |     |     |      |     |
| -                         |              |     |      |      |     |     |      |      |     |     |      | 603 |
| unknown (?)               |              |     |      |      |     |     |      |      |     |     |      | 1   |
| not sequenced             | 3            | 3   | 3    | 3    | 4   | 3   | 3    | 3    | 4   | 11  | 28   | 89  |
| sum of seq <sup>1</sup>   | 35           | 35  | 35   | 35   | 34  | 35  | 35   | 35   | 34  | 27  | 7    |     |
| oomcaa <sup>3</sup>       | 35           | 31  | 35   | 35   | 30  | 28  | 35   | 35   | 33  | 24  | 7    |     |
| mcaa <sup>4</sup>         | G            | G   | G    | T    | K   | L   | T    | V    | L   | G   | Q    |     |
| rel. oomcaa <sup>5</sup>  | 100%         | 89% | 100% | 100% | 88% | 80% | 100% | 100% | 97% | 89% | 100% |     |
| pos occupied <sup>6</sup> | 1            | 2   | 1    | 1    | 3   | 2   | 1    | 1    | 2   | 3   | 1    |     |

Table 5C: Analysis of V lambda subgroup 3

|                           | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|
| amino acid <sup>1</sup>   | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D   | E    | F   | 96  | 97  | 98   |
| A                         |         |     |      |     | 13  | 3   | 2   |     |     | 1   | 2   |     |     |     |      |     | 4   |     |      |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| C                         |         |     | 38   |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| D                         |         |     |      |     |     |     | 32  | 1   | 1   |     | 6   |     |     |     |      |     |     |     |      |
| E                         |         |     |      | 1   |     |     |     |     |     |     |     | 2   |     |     |      |     | 2   |     |      |
| F                         |         | 2   |      |     |     |     |     | 2   |     |     |     |     |     |     |      |     |     |     | 35   |
| G                         |         |     |      |     |     |     |     |     | 3   | 14  | 3   |     |     | 1   |      |     | 3   | 1   |      |
| H                         |         |     |      |     |     |     |     |     |     |     |     | 12  | 1   |     |      |     |     |     |      |
| I                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     | 4   |      |
| K                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |     |      |     |     |     |      |
| L                         |         |     |      | 1   |     |     |     | 1   |     | 1   |     | 1   | 1   |     |      |     | 4   | 2   |      |
| M                         |         |     |      |     |     |     |     |     | 1   |     |     |     |     |     |      |     | 1   | 1   |      |
| N                         |         |     |      | 10  |     |     | 2   | 1   | 2   |     | 10  | 1   |     |     |      |     |     |     |      |
| P                         |         |     |      |     |     |     |     |     | 1   |     |     |     | 3   |     |      |     | 1   |     |      |
| Q                         |         |     |      | 25  |     |     |     |     |     | 1   | 1   |     |     |     |      |     |     |     |      |
| R                         |         |     |      |     | 10  |     |     | 1   | 2   |     |     | 2   |     |     |      |     |     |     |      |
| S                         |         |     |      | 1   | 14  | 1   |     | 28  | 26  | 13  |     | 1   |     |     |      | 1   |     |     |      |
| T                         |         |     |      |     |     | 1   |     | 3   |     | 7   | 2   |     |     |     |      |     |     |     |      |
| V                         |         |     |      |     | 11  |     |     |     |     |     |     |     |     |     |      |     | 18  | 28  |      |
| W                         |         |     |      |     |     | 23  |     |     |     |     |     |     |     |     |      |     | 1   |     |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| Y                         | 38      | 36  |      |     |     |     | 1   |     | 1   |     | 1   | 3   | 1   |     |      |     | 3   |     |      |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| -                         |         |     |      |     |     |     |     |     |     |     | 10  | 15  | 31  | 36  | 37   | 36  |     | 1   |      |
| unknown (?)               |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| not sequenced             |         |     |      |     |     |     | 1   | 1   | 1   | 1   | 2   | 1   | 1   | 1   | 1    | 1   | 1   | 1   | 3    |
| sum of seq <sup>7</sup>   | 38      | 38  | 38   | 38  | 38  | 38  | 37  | 37  | 37  | 37  | 36  | 37  | 37  | 37  | 37   | 37  | 37  | 37  | 35   |
| oomcaa <sup>8</sup>       | 38      | 36  | 38   | 25  | 14  | 23  | 32  | 28  | 26  | 14  | 10  | 15  | 31  | 36  | 37   | 36  | 18  | 28  | 35   |
| mcaa <sup>9</sup>         | Y       | Y   | C    | Q   | S   | W   | D   | S   | S   | G   | N   | -   | -   | -   | -    | -   | V   | V   | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 95% | 100% | 66% | 37% | 61% | 86% | 76% | 70% | 38% | 28% | 41% | 84% | 97% | 100% | 97% | 49% | 76% | 100% |
| pos occupied <sup>6</sup> | 1       | 2   | 1    | 5   | 3   | 5   | 4   | 7   | 8   | 6   | 9   | 8   | 5   | 2   | 1    | 2   | 9   | 6   | 1    |

Table 5C: Analysis of V lambda subgroup 3

| Framework III             |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
|---------------------------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|--|
| amino acid <sup>1</sup>   | 67  | 68  | 69  | 70  | 71  | 72  | 73   | 74  | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82   | 83   | 84   | 85  |  |
| A                         |     |     |     | 1   | 36  | 1   |      | 1   |     |     |     | 11  | 1   | 34  |     |      |      | 38   |     |  |
| B                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| C                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| D                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     | 38   |      |      | 37  |  |
| E                         |     |     |     |     |     |     |      |     |     |     |     |     | 10  |     | 14  |      | 38   |      | 1   |  |
| F                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| G                         |     | 37  |     |     |     |     |      |     |     |     | 28  |     |     |     | 10  |      |      |      |     |  |
| H                         |     |     | 1   |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| I                         |     |     |     |     |     | 1   |      | 1   | 37  | 1   |     |     |     |     | 1   |      |      |      |     |  |
| K                         |     |     | 1   |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| L                         |     |     |     |     |     |     | 38   |     |     |     |     |     |     |     |     | 2    |      |      |     |  |
| M                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     | 10  |      |      |      |     |  |
| N                         |     |     | 28  |     |     |     |      |     |     | 1   |     |     |     |     |     |      |      |      |     |  |
| P                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| Q                         |     | 1   |     |     |     |     |      |     |     |     |     |     | 25  |     |     |      |      |      |     |  |
| R                         |     |     |     |     |     |     |      |     |     | 1   | 10  |     | 1   |     |     |      |      |      |     |  |
| S                         | 37  |     | 2   |     |     | 11  |      |     |     | 23  |     |     |     | 1   |     |      |      |      |     |  |
| T                         | 1   |     | 6   | 37  |     | 25  |      | 36  |     | 12  |     | 13  |     | 2   |     |      |      |      |     |  |
| V                         |     |     |     |     | 2   |     |      |     | 1   |     |     | 14  | 1   | 1   | 1   |      |      |      |     |  |
| W                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| X                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| Y                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| Z                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| -                         |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| unknown (?)               |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| not sequenced             |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |  |
| sum of seq <sup>7</sup>   | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38   | 38   | 38  |  |
| oomcaa <sup>3</sup>       | 37  | 37  | 28  | 37  | 36  | 25  | 38   | 36  | 37  | 23  | 28  | 14  | 25  | 34  | 14  | 38   | 38   | 38   | 37  |  |
| mcaa <sup>4</sup>         | S   | G   | N   | T   | A   | T   | L    | T   | I   | S   | G   | V   | Q   | A   | E   | D    | E    | A    | D   |  |
| rel. oomcaa <sup>5</sup>  | 97% | 97% | 74% | 97% | 95% | 66% | 100% | 95% | 97% | 61% | 74% | 37% | 66% | 89% | 37% | 100% | 100% | 100% | 97% |  |
| pos occupied <sup>6</sup> | 2   | 2   | 5   | 2   | 2   | 4   | 1    | 3   | 2   | 5   | 2   | 3   | 5   | 4   | 6   | 1    | 1    | 1    | 2   |  |

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Table 5C: Analysis of V lambda subgroup 3

|                           |     | CDR II |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
|---------------------------|-----|--------|------|------|------|------|------|------|------|-----|-----|------|------|------|------|------|-----|------|------|
| amino acid <sup>1</sup>   | 55  | 56     | A    | B    | C    | D    | E    | 57   | 58   | 59  | 60  | 61   | 62   | 63   | 64   | 65   | 66  | A    | B    |
| A                         |     | 1      |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| B                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| C                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| D                         |     |        |      |      |      |      |      |      |      |     | 9   |      |      |      |      |      |     |      |      |
| E                         |     |        |      |      |      |      |      |      |      |     | 27  |      |      |      |      |      |     |      |      |
| F                         |     |        |      |      |      |      |      |      |      |     |     |      | 38   |      |      |      |     |      |      |
| G                         |     |        |      |      |      |      |      | 38   |      |     |     |      |      |      | 38   |      |     |      |      |
| H                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| I                         |     |        |      |      |      |      |      |      | 37   |     |     |      |      |      |      |      |     |      |      |
| K                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| L                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| M                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| N                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      | 21  |      |      |
| P                         | 37  | 1      |      |      |      |      |      |      |      | 36  |     |      |      |      |      |      |     |      |      |
| Q                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| R                         |     |        |      |      |      |      |      |      |      |     |     | 38   |      |      |      |      |     |      |      |
| S                         | 1   | 36     |      |      |      |      |      |      |      | 1   |     |      |      | 38   |      | 38   | 12  |      |      |
| T                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      | 5   |      |      |
| V                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| W                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| X                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| Y                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| Z                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| -                         |     |        | 38   | 38   | 38   | 38   | 38   |      |      |     |     |      |      |      |      |      |     | 38   | 38   |
| unknown (?)               |     |        |      |      |      |      |      |      |      |     | 1   |      |      |      |      |      |     |      |      |
| not sequenced             |     |        |      |      |      |      |      |      | 1    | 1   | 1   |      |      |      |      |      |     |      |      |
| sum of seq <sup>7</sup>   | 38  | 38     | 38   | 38   | 38   | 38   | 38   | 38   | 37   | 37  | 37  | 38   | 38   | 38   | 38   | 38   | 38  | 38   | 38   |
| oomcaa <sup>3</sup>       | 37  | 36     | 38   | 38   | 38   | 38   | 38   | 38   | 37   | 36  | 27  | 38   | 38   | 38   | 38   | 38   | 21  | 38   | 38   |
| mcaa <sup>4</sup>         | P   | S      | -    | -    | -    | -    | -    | G    | I    | P   | E   | R    | F    | S    | G    | S    | N   | -    | -    |
| rel. oomcaa <sup>5</sup>  | 97% | 95%    | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 97% | 73% | 100% | 100% | 100% | 100% | 100% | 55% | 100% | 100% |
| pos occupied <sup>6</sup> | 2   | 3      | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 3   | 1    | 1    |



Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework II |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|----|----|----|----|----|
|                           | 36           | 37  | 38  | 39  | 40  | 41  | 42  | 43  | 44   | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | 53  | 54   |    |    |    |    |    |
| A                         |              |     |     |     |     |     |     | 23  |      |     |     |     |     |     |     | 1   |     | 1   |      |    |    |    |    |    |
| B                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| C                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| D                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     | 9   | 22  | 2   | 8   |      |    |    |    |    |    |
| E                         |              |     | 1   |     |     |     |     |     |      |     |     |     |     |     | 5   | 3   |     | 3   |      |    |    |    |    |    |
| F                         | 3            |     |     |     |     |     |     |     |      |     |     |     |     | 2   |     |     | 1   |     |      |    |    |    |    |    |
| G                         |              |     |     |     |     | 36  |     |     |      |     |     |     |     |     | 9   | 2   |     |     |      |    |    |    |    |    |
| H                         |              |     |     |     |     |     | 1   |     |      |     |     |     |     | 1   | 3   |     |     | 1   |      |    |    |    |    |    |
| I                         |              |     |     |     |     |     |     |     |      | 1   |     |     | 28  |     |     |     | 1   |     |      |    |    |    |    |    |
| K                         |              |     |     | 32  |     |     |     |     |      |     |     |     |     |     | 2   | 6   | 1   | 13  |      |    |    |    |    |    |
| L                         |              |     | 2   |     |     |     |     |     |      | 6   | 33  | 1   |     |     |     |     |     |     |      |    |    |    |    |    |
| M                         |              |     |     |     |     |     |     |     |      |     | 1   |     | 1   |     |     |     |     |     |      |    |    |    |    |    |
| N                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 1   | 19  | 9   |      |    |    |    |    |    |
| P                         |              |     |     |     | 36  |     | 1   |     | 38   |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| Q                         |              | 37  | 35  | 1   |     |     | 36  |     |      |     |     |     |     |     | 9   |     |     | 1   |      |    |    |    |    |    |
| R                         |              | 1   |     | 4   |     | 2   |     |     |      |     |     |     |     |     | 1   | 1   |     | 1   | 38   |    |    |    |    |    |
| S                         |              |     |     | 1   | 2   |     |     | 14  |      |     |     |     |     |     |     |     | 10  | 1   |      |    |    |    |    |    |
| T                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 2   | 4   |     |      |    |    |    |    |    |
| V                         |              |     |     |     |     |     |     | 1   |      | 31  | 4   | 37  | 9   |     |     |     |     |     |      |    |    |    |    |    |
| W                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| X                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| Y                         | 35           |     |     |     |     |     |     |     |      |     |     |     |     | 35  |     |     |     |     |      |    |    |    |    |    |
| Z                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| -                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| unknown (?)               |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| not sequenced             |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |    |    |    |    |    |
| sum of seq <sup>2</sup>   | 38           | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38 | 38 | 38 | 38 | 38 |
| oomcaa <sup>1</sup>       | 35           | 37  | 35  | 32  | 36  | 36  | 36  | 23  | 38   | 31  | 33  | 37  | 28  | 35  | 9   | 22  | 19  | 13  | 38   |    |    |    |    |    |
| mcaa <sup>1</sup>         | Y            | Q   | Q   | K   | P   | G   | Q   | A   | P    | V   | L   | V   | I   | Y   | D   | D   | N   | K   | R    |    |    |    |    |    |
| rel. oomcaa <sup>3</sup>  | 92%          | 97% | 92% | 84% | 95% | 95% | 95% | 61% | 100% | 82% | 87% | 97% | 74% | 92% | 24% | 58% | 50% | 34% | 100% |    |    |    |    |    |
| pos occupied <sup>4</sup> | 2            | 2   | 3   | 4   | 2   | 2   | 3   | 3   | 1    | 3   | 3   | 2   | 3   | 3   | 7   | 8   | 7   | 9   | 1    |    |    |    |    |    |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | CDRI |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |
|---------------------------|------|------|-----|------|-----|------|-----|-----|------|------|-----|-----|-----|-----|------|-----|-----|-----|------|
|                           | 20   | 21   | 22  | 23   | 24  | 25   | 26  | 27  | D    | E    | 28  | 29  | 30  | 31  | A    | 32  | 33  | 34  | 35   |
| A                         |      |      | 1   |      |     |      |     | 5   |      |      |     |     | 1   | 1   |      |     | 21  | 3   |      |
| B                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |
| C                         |      |      |     | 38   |     |      |     |     |      |      |     |     |     |     |      |     |     | 5   |      |
| D                         |      |      |     |      |     |      | 30  | 1   |      |      |     |     | 10  |     |      | 3   |     | 1   |      |
| E                         |      |      |     |      |     |      | 2   | 2   |      |      |     | 1   | 3   | 6   |      |     |     |     |      |
| F                         |      |      |     |      |     |      |     |     |      |      |     |     |     | 1   |      | 2   |     |     |      |
| G                         |      |      |     |      | 9   | 38   |     | 1   |      |      |     | 23  | 4   |     |      |     |     |     |      |
| H                         |      |      |     |      |     |      | 1   |     |      |      |     |     |     |     |      | 2   |     | 9   |      |
| I                         |      | 38   |     |      |     |      |     |     |      |      | 9   |     |     | 1   |      |     |     |     |      |
| K                         |      |      |     |      |     |      |     | 7   |      |      |     |     | 2   | 13  |      |     |     |     |      |
| L                         |      |      |     |      |     |      |     |     |      |      | 28  |     |     |     |      |     |     |     |      |
| M                         | 1    |      |     |      |     |      |     |     |      |      |     |     |     | 1   |      |     |     |     |      |
| N                         |      |      | 2   |      |     |      | 4   | 9   |      |      | 1   |     | 2   |     |      | 1   |     | 2   |      |
| P                         |      |      | 1   |      |     |      |     |     |      |      |     | 3   |     |     |      |     |     |     |      |
| Q                         |      |      |     |      | 10  |      |     |     |      |      |     |     |     | 4   |      |     |     |     |      |
| R                         | 25   |      |     |      |     |      |     | 2   |      |      |     | 10  | 1   |     |      |     | 1   |     |      |
| S                         | 9    |      | 1   |      | 19  |      |     | 10  |      |      |     |     | 11  | 2   |      | 8   |     | 14  |      |
| T                         | 3    |      | 33  |      |     |      |     | 1   |      |      |     | 1   | 4   |     |      |     |     |     |      |
| V                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      | 1   | 15  |     |      |
| W                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     | 38   |
| X                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |
| Y                         |      |      |     |      |     |      | 1   |     |      |      |     |     |     | 8   |      | 20  | 1   | 4   |      |
| Z                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |
| -                         |      |      |     |      |     |      |     | 38  | 38   |      |     |     |     |     | 37   |     |     |     |      |
| unknown (?)               |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |
| not sequenced             |      |      |     |      |     |      |     |     |      |      |     |     |     |     | 1    | 1   |     |     |      |
| sum of seq <sup>2</sup>   | 38   | 38   | 38  | 38   | 38  | 38   | 38  | 38  | 38   | 38   | 38  | 38  | 38  | 37  | 37   | 37  | 38  | 38  | 38   |
| oomcaa <sup>1</sup>       | 25   | 38   | 33  | 38   | 19  | 38   | 30  | 10  | 38   | 38   | 28  | 23  | 11  | 13  | 37   | 20  | 21  | 14  | 38   |
| mcaa <sup>1</sup>         | R    | I    | T   | C    | S   | G    | D   | S   | -    | -    | L   | G   | S   | K   | -    | Y   | A   | S   | W    |
| rel. oomcaa <sup>2</sup>  | 66%  | 100% | 87% | 100% | 50% | 100% | 79% | 26% | 100% | 100% | 74% | 61% | 29% | 35% | 100% | 54% | 55% | 37% | 100% |
| pos occupied <sup>3</sup> | 4    | 1    | 5   | 1    | 3   | 1    | 5   | 9   | 1    | 1    | 3   | 5   | 9   | 9   | 1    | 7   | 4   | 7   | 1    |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework I |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
|---------------------------|-------------|-----|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|------|-----|
|                           | 1           | 2   | 3   | 4   | 5   | 6    | 7   | 8   | 9   | 10   | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18   | 19  |
| A                         |             |     |     |     | 1   |      | 1   | 2   | 7   |      |     |     |     | 20  | 1   |     |     |      | 27  |
| B                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| C                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| D                         |             |     | 5   |     |     |      | 10  |     |     |      |     |     |     |     |     |     |     |      |     |
| E                         |             |     | 20  |     |     |      |     |     |     |      |     |     | 1   |     |     | 1   |     |      |     |
| F                         | 1           | 1   |     |     |     |      |     |     |     |      |     | 1   |     |     | 1   |     |     |      |     |
| G                         |             |     | 1   |     |     |      |     |     |     |      |     |     |     |     |     | 37  |     |      |     |
| H                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| I                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| K                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     | 2   |      |     |
| L                         |             |     |     | 37  |     |      |     |     |     |      | 4   |     | 1   |     | 9   |     |     |      |     |
| M                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| N                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| P                         |             |     |     |     |     |      | 26  | 35  | 1   |      |     |     |     |     | 27  |     |     |      | 1   |
| Q                         | 4           |     | 4   |     |     | 38   |     |     |     |      |     |     |     |     |     |     | 36  |      |     |
| R                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| S                         | 13          | 14  |     |     | 1   |      | 1   |     | 28  |      |     | 37  |     | 18  |     |     |     |      |     |
| T                         |             |     |     |     | 36  |      |     | 1   |     |      |     |     |     |     |     |     |     | 38   |     |
| V                         |             |     | 8   | 1   |     |      |     |     | 2   |      | 34  |     | 36  |     |     |     |     |      | 10  |
| W                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| X                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| Y                         |             | 23  |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| Z                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| -                         | 20          |     |     |     |     |      |     |     |     | 38   |     |     |     |     |     |     |     |      |     |
| unknown (?)               |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| not sequenced             |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 38          | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38  |
| oomcaa <sup>3</sup>       | 20          | 23  | 20  | 37  | 36  | 38   | 26  | 35  | 28  | 38   | 34  | 37  | 36  | 20  | 27  | 37  | 36  | 38   | 27  |
| mcaa <sup>4</sup>         | -           | Y   | E   | L   | T   | Q    | P   | P   | S   | -    | V   | S   | V   | A   | P   | G   | Q   | T    | A   |
| rel. oomcaa <sup>5</sup>  | 53%         | 61% | 53% | 97% | 95% | 100% | 68% | 92% | 74% | 100% | 89% | 97% | 95% | 53% | 71% | 97% | 95% | 100% | 71% |
| pos occupied <sup>6</sup> | 4           | 3   | 5   | 2   | 3   | 1    | 4   | 3   | 4   | 1    | 2   | 2   | 3   | 2   | 4   | 2   | 2   | 1    | 3   |

Table 5B: Analysis of V lambda subgroup 2

| Framework IV              |      |     |      |      |     |     |     |      |     |     |      |     |
|---------------------------|------|-----|------|------|-----|-----|-----|------|-----|-----|------|-----|
| amino acid <sup>1</sup>   | 99   | 100 | 101  | 102  | 103 | 104 | 105 | 106  | A   | 107 | 108  | sum |
| A                         |      | 1   |      |      |     |     |     |      |     |     |      | 280 |
| B                         |      |     |      |      |     |     |     |      |     |     |      |     |
| C                         |      |     |      |      |     |     |     |      |     |     |      | 99  |
| D                         |      |     |      |      |     |     |     |      |     |     |      | 188 |
| E                         |      |     |      |      |     |     |     |      |     |     |      | 107 |
| F                         |      |     |      |      |     |     |     |      |     |     |      | 113 |
| G                         | 42   | 33  | 42   |      |     |     |     |      |     | 19  |      | 567 |
| H                         |      |     |      |      |     |     |     |      |     |     |      | 48  |
| I                         |      |     |      |      |     |     | 1   |      |     |     |      | 184 |
| K                         |      |     |      |      | 36  |     |     |      |     |     |      | 189 |
| L                         |      |     |      |      |     | 28  |     |      | 40  |     |      | 264 |
| M                         |      |     |      |      |     |     |     |      |     |     |      | 29  |
| N                         |      |     |      |      | 1   |     |     |      |     |     |      | 146 |
| P                         |      |     |      |      |     |     |     |      |     |     |      | 238 |
| Q                         |      |     |      |      | 1   |     |     |      |     |     | 14   | 250 |
| R                         |      | 1   |      |      | 2   |     |     |      |     | 4   |      | 121 |
| S                         |      |     |      |      |     |     | 1   |      |     | 2   |      | 831 |
| T                         |      | 7   |      | 41   |     |     | 40  |      |     |     |      | 398 |
| V                         |      |     |      |      |     | 14  |     | 42   | 1   |     |      | 327 |
| W                         |      |     |      |      |     |     |     |      |     |     |      | 48  |
| X                         |      |     |      |      |     |     |     |      |     |     |      |     |
| Y                         |      |     |      |      | 1   |     |     |      |     |     |      | 285 |
| Z                         |      |     |      |      |     |     |     |      |     |     |      | 16  |
| -                         |      |     |      |      |     |     |     |      |     |     |      | 555 |
| unknown (?)               |      |     |      |      |     |     |     |      |     |     |      | 8   |
| not sequenced             | 1    | 1   | 1    | 2    | 2   | 1   | 1   | 1    | 2   | 15  | 28   | 80  |
| sum of seq <sup>2</sup>   | 42   | 42  | 42   | 41   | 41  | 42  | 42  | 42   | 41  | 25  | 14   |     |
| oomcaa <sup>3</sup>       | 42   | 33  | 42   | 41   | 36  | 28  | 40  | 42   | 40  | 19  | 14   |     |
| mcaa <sup>4</sup>         | G    | G   | G    | T    | K   | L   | T   | V    | L   | G   | Q    |     |
| rel. oomcaa <sup>5</sup>  | 100% | 79% | 100% | 100% | 88% | 67% | 95% | 100% | 98% | 76% | 100% |     |
| pos occupied <sup>6</sup> | 1    | 4   | 1    | 1    | 5   | 2   | 3   | 1    | 2   | 3   | 1    |     |

Table 5B: Analysis of V lambda subgroup 2

|                           | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|------|
| amino acid <sup>1</sup>   | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D    | E    | F    | 96  | 97  | 98   |
| A                         |         |     |      | 2   | 1   |     | 21  |     | 1   |     |     |     |     |      |      |      | 1   | 1   |      |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| C                         |         |     | 43   | 11  |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| D                         |         |     |      |     |     |     |     | 3   | 1   | 2   |     |     |     |      |      |      | 1   |     |      |
| E                         |         |     |      |     |     |     | 1   | 1   |     |     |     |     |     |      |      |      |     |     |      |
| F                         |         | 3   |      |     |     | 3   |     |     |     | 1   |     | 1   |     |      |      |      | 5   |     | 42   |
| G                         |         |     |      |     |     |     | 1   | 21  | 3   | 4   |     |     |     |      |      |      | 1   |     |      |
| H                         |         |     |      |     |     | 1   |     |     |     |     |     |     |     |      |      |      |     |     |      |
| I                         |         |     |      |     |     |     | 1   | 1   |     | 1   | 2   |     |     |      |      |      | 1   | 7   |      |
| K                         |         |     |      |     |     |     |     |     |     | 3   |     |     |     |      |      |      |     |     |      |
| L                         |         |     |      |     |     |     |     |     |     |     |     | 1   | 1   |      |      |      | 6   | 5   |      |
| M                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 1   | 1   |      |
| N                         |         |     |      |     |     |     |     |     | 5   | 7   | 5   |     |     |      |      |      | 1   |     |      |
| P                         |         |     |      |     |     |     |     | 1   |     |     |     | 4   |     |      |      |      |     |     |      |
| Q                         |         |     |      |     |     |     |     |     |     | 1   | 2   |     |     |      |      |      |     |     |      |
| R                         |         |     |      |     |     |     | 2   |     | 3   |     |     | 1   |     |      |      |      | 5   |     |      |
| S                         |         | 1   |      | 30  | 41  |     |     | 12  | 23  | 14  | 9   |     |     |      |      |      | 1   |     |      |
| T                         |         |     |      |     |     |     | 16  | 4   | 4   | 3   | 21  |     |     |      |      |      |     |     |      |
| V                         |         |     |      |     |     |     | 1   |     |     |     |     |     |     |      |      |      | 11  | 28  |      |
| W                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 5   |     |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| Y                         | 43      | 39  |      |     |     | 39  |     |     | 1   | 6   |     |     |     |      |      |      | 4   |     |      |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| -                         |         |     |      |     |     |     |     |     |     | 1   | 3   | 36  | 42  | 43   | 43   | 43   |     |     |      |
| unknown (?)               |         |     |      |     |     |     |     |     | 2   |     |     |     |     |      |      |      |     |     |      |
| not sequenced             |         |     |      |     | 1   |     |     |     |     |     | 1   |     |     |      |      |      |     | 1   | 1    |
| sum of seq <sup>2</sup>   | 43      | 43  | 43   | 43  | 42  | 43  | 43  | 43  | 43  | 43  | 42  | 43  | 43  | 43   | 43   | 43   | 43  | 42  | 42   |
| oomcaa <sup>3</sup>       | 43      | 39  | 43   | 30  | 41  | 39  | 21  | 21  | 23  | 14  | 21  | 36  | 42  | 43   | 43   | 43   | 11  | 28  | 42   |
| mcaa <sup>4</sup>         | Y       | Y   | C    | S   | S   | Y   | A   | G   | S   | S   | T   | -   | -   | -    | -    | -    | V   | V   | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 91% | 100% | 70% | 98% | 91% | 49% | 49% | 53% | 33% | 50% | 84% | 98% | 100% | 100% | 100% | 26% | 67% | 100% |
| pos occupied <sup>6</sup> | 1       | 3   | 1    | 3   | 2   | 3   | 7   | 7   | 8   | 11  | 6   | 5   | 2   | 1    | 1    | 1    | 13  | 5   | 1    |

Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | Framework III |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
|---------------------------|---------------|-----|-----|-----|------|------|------|------|-----|-----|-----|------|-----|-----|-----|-----|------|------|-----|
|                           | 67            | 68  | 69  | 70  | 71   | 72   | 73   | 74   | 75  | 76  | 77  | 78   | 79  | 80  | 81  | 82  | 83   | 84   | 85  |
| A                         |               | 3   |     | 1   | 43   |      |      |      |     |     |     |      |     | 36  |     |     |      | 43   |     |
| B                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| C                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| D                         |               | 1   | 2   |     |      |      |      |      |     |     |     |      |     |     | 3   | 42  |      |      | 39  |
| E                         |               |     |     |     |      |      |      |      |     |     | 1   |      |     |     | 38  |     | 43   |      |     |
| F                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| G                         |               | 39  |     |     |      |      |      |      |     |     | 42  |      |     |     | 1   |     |      |      |     |
| H                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      | 2   |
| I                         |               |     |     |     |      |      |      |      | 35  |     |     |      |     |     |     |     |      |      |     |
| K                         |               |     | 1   |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| L                         |               |     |     |     |      |      | 43   |      |     |     |     | 43   |     |     |     |     |      |      |     |
| M                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| N                         |               |     | 38  |     |      |      |      |      |     |     |     |      |     |     | 1   | 1   |      |      | 1   |
| P                         |               |     |     |     |      |      |      |      |     |     |     |      |     | 2   |     |     |      |      |     |
| Q                         |               |     |     |     |      |      |      |      |     |     |     |      | 41  |     |     |     |      |      |     |
| R                         |               |     |     |     |      |      |      |      |     |     |     |      | 2   |     |     |     |      |      |     |
| S                         | 42            |     |     | 1   |      | 43   |      |      |     | 42  |     |      |     |     |     |     |      |      |     |
| T                         |               |     | 1   | 41  |      |      |      | 43   |     | 1   |     |      |     | 2   |     |     |      |      |     |
| V                         |               |     |     |     |      |      |      |      | 8   |     |     |      |     | 3   |     |     |      |      |     |
| W                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| X                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| Y                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| Z                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| -                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| unknown (?)               |               |     | 1   |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      | 1   |
| not sequenced             | 1             |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| sum of seq <sup>2</sup>   | 42            | 43  | 43  | 43  | 43   | 43   | 43   | 43   | 43  | 43  | 43  | 43   | 43  | 43  | 43  | 43  | 43   | 43   | 43  |
| oomcaa <sup>3</sup>       | 42            | 39  | 38  | 41  | 43   | 43   | 43   | 43   | 35  | 42  | 42  | 43   | 41  | 36  | 38  | 42  | 43   | 43   | 39  |
| mcaa <sup>4</sup>         | S             | G   | N   | T   | A    | S    | L    | T    | I   | S   | G   | L    | Q   | A   | E   | D   | E    | A    | D   |
| rel. oomcaa <sup>5</sup>  | 100%          | 91% | 88% | 95% | 100% | 100% | 100% | 100% | 81% | 98% | 98% | 100% | 95% | 84% | 88% | 98% | 100% | 100% | 91% |
| pos occupied <sup>6</sup> | 1             | 3   | 4   | 3   | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 1    | 2   | 4   | 4   | 2   | 1    | 1    | 3   |

Table 5B: Analysis of V lambda subgroup 2

| CDR II                    |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
|---------------------------|------|------|------|------|------|------|------|------|-----|-----|-----|------|-----|------|-----|-----|-----|------|------|--|
| amino acid <sup>1</sup>   | 55   | 56   | A    | B    | C    | D    | E    | 57   | 58  | 59  | 60  | 61   | 62  | 63   | 64  | 65  | 66  | A    | B    |  |
| A                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      | 2   |     |     |      |      |  |
| B                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| C                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     | 1   |     |      |      |  |
| D                         |      |      |      |      |      |      |      |      |     |     | 17  |      |     |      |     |     |     |      |      |  |
| E                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| F                         |      |      |      |      |      |      |      |      |     |     |     |      | 42  |      |     |     |     |      |      |  |
| G                         |      |      |      |      |      |      |      | 43   | 1   |     |     |      |     |      | 41  |     |     |      |      |  |
| H                         |      |      |      |      |      |      |      |      |     |     | 2   |      |     |      |     |     |     |      |      |  |
| I                         |      |      |      |      |      |      |      |      | 3   |     |     |      |     |      |     |     |     |      |      |  |
| K                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     | 42  |      |      |  |
| L                         |      |      |      |      |      |      |      |      |     |     | 1   |      | 1   |      |     |     |     |      |      |  |
| M                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| N                         |      |      |      |      |      |      |      |      |     |     | 19  |      |     |      |     |     |     |      |      |  |
| P                         | 43   |      |      |      |      |      |      |      |     | 15  |     |      |     |      |     |     |     |      |      |  |
| Q                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| R                         |      |      |      |      |      |      |      |      |     |     |     | 43   |     |      |     |     | 1   |      |      |  |
| S                         |      | 43   |      |      |      |      |      |      |     | 28  | 2   |      |     | 43   |     | 42  |     |      |      |  |
| T                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| V                         |      |      |      |      |      |      |      |      | 39  |     |     |      |     |      |     |     |     |      |      |  |
| W                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| X                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| Y                         |      |      |      |      |      |      |      |      |     |     | 2   |      |     |      |     |     |     |      |      |  |
| Z                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| -                         |      |      | 43   | 43   | 43   | 43   | 43   |      |     |     |     |      |     |      |     |     |     | 43   | 43   |  |
| unknown (?)               |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| not sequenced             |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| sum of seq <sup>2</sup>   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43  | 43  | 43  | 43   | 43  | 43   | 43  | 43  | 43  | 43   | 43   |  |
| oomcaa <sup>3</sup>       | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 39  | 28  | 19  | 43   | 42  | 43   | 41  | 42  | 42  | 43   | 43   |  |
| mcaa <sup>4</sup>         | P    | S    | -    | -    | -    | -    | -    | G    | V   | S   | N   | R    | F   | S    | G   | S   | K   | -    | -    |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 91% | 65% | 44% | 100% | 98% | 100% | 95% | 98% | 98% | 100% | 100% |  |
| pos occupied <sup>6</sup> | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 3   | 2   | 6   | 1    | 2   | 1    | 2   | 2   | 2   | 1    | 1    |  |

Table 5B: Analysis of V lambda subgroup 2

|                           | Framework II |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|------|--|--|--|--|--|
| amino acid <sup>1</sup>   | 36           | 37  | 38  | 39  | 40  | 41  | 42  | 43  | 44   | 45  | 46  | 47  | 48   | 49  | 50  | 51  | 52  | 53  | 54   |  |  |  |  |  |
| A                         |              |     |     |     | 1   | 4   |     | 40  |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| B                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| C                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| D                         |              |     |     | 1   |     | 2   |     |     |      |     |     |     |      |     | 20  | 1   | 2   | 1   |      |  |  |  |  |  |
| E                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     | 20  |     |     | 2   |      |  |  |  |  |  |
| F                         | 2            |     |     |     |     |     |     |     |      |     |     |     |      | 7   |     | 1   |     |     |      |  |  |  |  |  |
| G                         |              |     |     |     |     | 36  |     |     |      |     |     |     |      |     | 2   | 2   |     | 1   |      |  |  |  |  |  |
| H                         |              |     | 2   | 34  |     |     |     |     |      |     |     |     |      |     |     |     |     | 1   |      |  |  |  |  |  |
| I                         | -            |     |     |     |     | 1   |     |     |      | 1   | 9   | 43  |      |     |     |     | 1   |     |      |  |  |  |  |  |
| K                         |              |     |     |     |     | 40  |     |     | 41   |     |     |     |      |     |     |     | 1   | 21  |      |  |  |  |  |  |
| L                         |              |     | 1   | 1   |     |     |     |     |      | 38  | 6   |     |      |     |     |     |     |     |      |  |  |  |  |  |
| M                         |              |     |     |     |     |     |     |     |      |     | 26  |     |      |     |     |     | 1   |     |      |  |  |  |  |  |
| N                         |              |     |     | 2   |     |     |     |     |      |     |     |     |      |     | 1   |     | 8   | 12  |      |  |  |  |  |  |
| P                         |              |     |     |     | 41  |     |     | 43  |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| Q                         |              | 41  | 39  |     |     |     |     |     |      | 2   |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| R                         |              | 1   |     |     |     | 1   |     |     |      |     |     |     |      |     |     |     | 2   | 43  |      |  |  |  |  |  |
| S                         |              |     |     |     | 1   |     |     |     |      |     |     |     |      | 2   |     |     | 21  | 3   |      |  |  |  |  |  |
| T                         |              |     |     |     |     | 1   |     |     |      |     |     |     |      |     |     |     | 7   |     |      |  |  |  |  |  |
| V                         |              |     |     |     |     | 1   |     | 3   |      |     | 4   | 2   |      |     |     | 39  |     |     |      |  |  |  |  |  |
| W                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| X                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| Y                         | 41           |     |     | 5   |     |     |     |     |      |     |     |     |      | 34  |     |     |     | 2   |      |  |  |  |  |  |
| Z                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| -                         |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| unknown (?)               |              | 1   | 1   |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| not sequenced             |              |     |     |     |     |     |     |     |      |     |     |     |      |     |     |     |     |     |      |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 43           | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43   | 43  | 43  | 43  | 43   | 43  | 43  | 43  | 43  | 43  | 43   |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 41           | 41  | 39  | 34  | 41  | 36  | 40  | 40  | 43   | 41  | 38  | 26  | 43   | 34  | 20  | 39  | 21  | 21  | 43   |  |  |  |  |  |
| mcaa <sup>4</sup>         | Y            | Q   | Q   | H   | P   | G   | K   | A   | P    | K   | L   | M   | I    | Y   | D   | V   | S   | K   | R    |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 95%          | 95% | 91% | 79% | 95% | 84% | 93% | 93% | 100% | 95% | 88% | 60% | 100% | 79% | 47% | 91% | 49% | 49% | 100% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 2   | 3   | 5   | 3   | 4   | 4   | 2   | 1    | 2   | 3   | 4   | 1    | 3   | 4   | 4   | 8   | 8   | 1    |  |  |  |  |  |



Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | CDRI |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
|---------------------------|------|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
|                           | 20   | 21  | 22   | 23   | 24  | 25   | 26  | 27  | D   | E   | 28  | 29  | 30  | 31  | A   | 32  | 33  | 34   | 35   |
| A                         |      |     |      |      | 3   |      | 1   |     |     |     |     |     | 1   |     |     | 1   |     |      |      |
| B                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| C                         |      |     |      | 42   |     |      |     |     | 1   |     |     |     |     | 1   |     |     |     |      |      |
| D                         |      |     |      |      |     |      |     |     | 39  |     |     | 1   | 4   |     |     | 5   |     |      |      |
| E                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |      |      |
| F                         |      | 1   |      |      |     |      |     |     |     |     |     |     | 1   |     |     |     | 4   |      |      |
| G                         |      |     |      |      |     | 43   |     | 1   |     |     |     | 39  | 26  |     |     |     |     |      |      |
| H                         |      |     |      |      |     |      |     | 1   |     |     |     |     |     |     | 1   | 1   |     |      |      |
| I                         |      | 41  |      |      | 1   |      |     |     |     |     | 6   |     |     |     |     |     |     |      |      |
| K                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 4   |     |     |      |      |
| L                         |      | 1   |      |      |     |      |     |     |     |     |     |     |     |     |     | 4   |     |      |      |
| M                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| N                         |      |     |      |      |     |      |     | 1   | 3   | 4   |     | 1   | 4   | 3   | 28  |     |     |      |      |
| P                         |      |     |      |      |     |      |     | 1   |     |     |     |     |     |     |     |     |     |      |      |
| Q                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| R                         |      |     |      |      |     |      |     |     | 1   |     |     |     | 2   |     |     |     |     |      |      |
| S                         |      |     | 42   |      | 3   |      | 3   | 35  | 38  |     |     |     | 5   | 1   | 2   | 4   | 1   | 42   |      |
| T                         | 43   |     |      |      | 36  |      | 39  | 3   |     |     |     | 1   |     | 1   |     |     |     |      |      |
| V                         |      |     |      |      |     |      |     |     |     |     | 37  |     |     |     |     |     | 41  |      |      |
| W                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      | 43   |
| X                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| Y                         |      |     |      |      |     |      |     | 1   |     |     |     | 1   |     | 37  |     | 29  |     |      |      |
| Z                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| -                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 1   |     |     |      |      |
| unknown (?)               |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 1   |     |     |      |      |
| not sequenced             |      |     | 1    | 1    |     |      |     |     |     |     |     |     |     |     |     |     | 1   | 1    |      |
| sum of seq <sup>2</sup>   | 43   | 43  | 42   | 42   | 43  | 43   | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 42  | 42   | 43   |
| oomcaa <sup>3</sup>       | 43   | 41  | 42   | 42   | 36  | 43   | 39  | 35  | 38  | 39  | 37  | 39  | 26  | 37  | 28  | 29  | 41  | 42   | 43   |
| mcaa <sup>4</sup>         | T    | I   | S    | C    | T   | G    | T   | S   | S   | D   | V   | G   | G   | Y   | N   | Y   | V   | S    | W    |
| rel. oomcaa <sup>5</sup>  | 100% | 95% | 100% | 100% | 84% | 100% | 91% | 81% | 88% | 91% | 86% | 91% | 60% | 86% | 65% | 67% | 98% | 100% | 100% |
| pos occupied <sup>6</sup> | 1    | 3   | 1    | 1    | 4   | 1    | 3   | 7   | 4   | 2   | 2   | 5   | 7   | 5   | 7   | 6   | 2   | 1    | 1    |

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Table 5B: Analysis of V lambda subgroup 2

| Framework I               |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
|---------------------------|-----|-----|-----|------|------|-----|------|-----|-----|------|-----|------|-----|-----|-----|-----|-----|------|-----|
| amino acid <sup>1</sup>   | 1   | 2   | 3   | 4    | 5    | 6   | 7    | 8   | 9   | 10   | 11  | 12   | 13  | 14  | 15  | 16  | 17  | 18   | 19  |
| A                         |     |     | 35  |      |      |     |      | 30  |     |      | 6   |      | 1   | 1   |     |     |     |      |     |
| B                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| C                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| D                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     | 1   |     |      |     |
| E                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| F                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| G                         |     |     |     |      |      |     |      |     |     |      |     |      | 42  |     |     | 42  |     |      |     |
| H                         | 2   |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     | 1   |      |     |
| I                         |     |     | 1   |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      | 28  |
| K                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| L                         |     |     |     | 40   |      |     |      |     |     |      |     |      |     |     | 3   |     |     |      | 1   |
| M                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| N                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| P                         |     |     |     |      |      |     | 42   | 6   |     |      |     |      |     |     | 40  |     |     |      |     |
| Q                         | 22  |     | 4   |      |      | 41  |      |     |     |      |     |      |     |     |     |     | 42  |      |     |
| R                         |     |     |     |      |      |     |      | 6   | 1   |      |     |      |     |     |     |     |     |      |     |
| S                         |     | 41  |     |      |      |     |      |     | 40  |      |     | 42   |     | 42  |     |     |     | 43   |     |
| T                         |     |     |     |      | 42   |     |      |     | 1   |      |     |      |     |     |     |     |     |      |     |
| V                         |     | 1   | 2   |      |      |     |      |     |     |      | 36  |      |     |     |     |     |     |      | 14  |
| W                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| X                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| Y                         |     |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| Z                         | 16  |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| -                         |     |     |     |      |      |     |      |     |     | 42   |     |      |     |     |     |     |     |      |     |
| unknown (?)               |     |     |     |      |      | 1   |      |     |     |      |     |      |     |     |     |     |     |      |     |
| not sequenced             | 3   | 1   | 1   | 3    | 1    | 1   | 1    | 1   | 1   | 1    | 1   | 1    |     |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 40  | 42  | 42  | 40   | 42   | 42  | 42   | 42  | 42  | 42   | 42  | 42   | 43  | 43  | 43  | 43  | 43  | 43   | 43  |
| oomcaa <sup>3</sup>       | 22  | 41  | 35  | 40   | 42   | 41  | 42   | 30  | 40  | 42   | 36  | 42   | 42  | 42  | 40  | 42  | 42  | 43   | 28  |
| mcaa <sup>4</sup>         | Q   | S   | A   | L    | T    | Q   | P    | A   | S   | -    | V   | S    | G   | S   | P   | G   | Q   | S    | I   |
| rel. oomcaa <sup>5</sup>  | 55% | 98% | 83% | 100% | 100% | 98% | 100% | 71% | 95% | 100% | 86% | 100% | 98% | 98% | 93% | 98% | 98% | 100% | 65% |
| pos occupied <sup>6</sup> | 3   | 2   | 4   | 1    | 1    | 1   | 1    | 3   | 3   | 1    | 2   | 1    | 2   | 2   | 2   | 2   | 2   | 1    | 3   |

Table 5A: Analysis of V lambda subgroup 1

| Framework IV              |      |     |      |      |     |     |      |      |     |     |     |     |
|---------------------------|------|-----|------|------|-----|-----|------|------|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 99   | 100 | 101  | 102  | 103 | 104 | 105  | 106  | A   | 107 | 108 | sum |
| A                         |      |     |      |      |     |     |      |      |     |     |     | 285 |
| B                         |      |     |      |      |     |     |      |      |     |     |     |     |
| C                         |      |     |      |      |     |     |      |      |     |     |     | 84  |
| D                         |      |     |      |      |     |     |      |      |     |     |     | 224 |
| E                         |      | 1   |      |      |     |     |      |      |     |     |     | 81  |
| F                         |      |     |      |      |     |     |      |      |     |     |     | 87  |
| G                         | 36   | 31  | 36   |      |     |     |      |      |     | 26  |     | 559 |
| H                         |      |     |      |      |     |     |      |      |     |     |     | 25  |
| I                         |      |     |      |      |     |     |      |      |     |     |     | 188 |
| K                         |      |     |      |      | 30  |     |      |      |     |     |     | 141 |
| L                         |      |     |      |      |     | 25  |      |      | 34  |     |     | 344 |
| M                         |      |     |      |      |     |     |      |      |     |     |     | 5   |
| N                         |      |     |      |      | 1   |     |      |      |     |     |     | 176 |
| P                         |      |     |      |      |     |     |      |      |     |     | 1   | 296 |
| Q                         |      |     |      |      | 3   |     |      |      | 1   | 18  |     | 251 |
| R                         |      |     |      |      | 1   |     |      |      |     | 2   |     | 156 |
| S                         |      | 1   |      |      |     |     |      |      |     | 2   |     | 720 |
| T                         |      | 3   |      | 36   | 1   |     | 36   |      |     |     |     | 359 |
| V                         |      |     |      |      |     | 11  |      | 36   | 1   |     |     | 282 |
| W                         |      |     |      |      |     |     |      |      |     | 1   |     | 92  |
| X                         |      |     |      |      |     |     |      |      |     |     |     |     |
| Y                         |      |     |      |      |     |     |      |      |     |     |     | 202 |
| Z                         |      |     |      |      |     |     |      |      |     |     |     | 16  |
| -                         |      |     |      |      |     |     |      |      |     |     |     | 524 |
| unknown (?)               |      |     |      |      |     |     |      |      |     |     |     |     |
| not sequenced             | 4    | 6   | 6    | 6    | 6   | 6   | 6    | 6    | 6   | 10  | 22  | 141 |
| sum of seq <sup>2</sup>   | 36   | 36  | 36   | 36   | 36  | 36  | 36   | 36   | 36  | 31  | 19  |     |
| oomcaa <sup>3</sup>       | 36   | 31  | 36   | 36   | 30  | 25  | 36   | 36   | 34  | 26  | 18  |     |
| mcaa <sup>4</sup>         | G    | G   | G    | T    | K   | L   | T    | V    | L   | G   | Q   |     |
| rel. oomcaa <sup>5</sup>  | 100% | 86% | 100% | 100% | 83% | 69% | 100% | 100% | 94% | 84% | 95% |     |
| pos occupied <sup>6</sup> | 1    | 4   | 1    | 1    | 5   | 2   | 1    | 1    | 3   | 4   | 2   |     |

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Table 5A: Analysis of V lambda subgroup 1

|                           | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|------|
| amino acid <sup>1</sup>   | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D    | E    | F    | 96  | 97  | 98   |
| A                         |         |     |      | 22  | 15  |     |     | 1   |     |     |     | 16  |     |      |      |      | 4   | 1   |      |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| C                         |         |     | 42   |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| D                         |         |     |      |     |     |     | 39  | 17  |     |     | 7   |     |     |      |      |      |     |     |      |
| E                         |         |     |      |     |     |     |     |     |     |     |     | 1   |     |      |      |      | 1   |     |      |
| F                         |         | 2   |      |     |     |     |     |     |     | 1   |     |     |     |      |      |      |     |     | 36   |
| G                         |         |     |      | 14  |     |     |     | 1   |     |     |     | 17  | 1   |      |      |      | 5   | 1   |      |
| H                         |         | 1   |      |     |     |     |     |     |     |     |     |     | 1   |      |      |      |     |     |      |
| I                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     | 1   |      |
| K                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     |     |      |
| L                         |         |     |      | 1   |     |     |     |     |     | 37  |     |     | 1   |      |      |      |     | 1   |      |
| M                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     | 1   |      |
| N                         |         |     |      |     |     |     | 2   | 2   |     |     | 9   | 1   |     |      |      |      |     |     |      |
| P                         |         |     |      |     |     |     |     |     |     | 1   |     |     |     |      |      |      | 6   |     |      |
| Q                         |         |     |      | 3   |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| R                         |         |     |      |     |     |     |     |     | 5   | 1   | 2   |     |     |      |      |      | 2   |     |      |
| S                         |         |     |      |     | 4   |     |     | 17  | 35  |     | 18  |     | 1   |      |      |      | 1   |     |      |
| T                         |         |     |      |     | 22  |     |     | 1   | 1   |     | 1   |     |     |      |      |      |     |     |      |
| V                         |         |     |      | 1   |     |     |     | 1   |     | 1   |     | 2   |     |      |      |      | 9   | 34  |      |
| W                         |         |     |      |     |     | 38  |     |     |     |     |     |     |     |      |      |      | 7   |     |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| Y                         | 42      | 39  |      |     |     | 3   |     | 1   |     |     |     |     |     |      |      |      | 3   |     |      |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| -                         |         |     |      |     |     |     |     |     |     |     | 2   | 4   | 35  | 39   | 38   | 38   | 1   |     |      |
| unknown (?)               |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| not sequenced             |         |     |      | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 3   | 3    | 3    | 3    | 3   | 3   | 4    |
| sum of seq <sup>2</sup>   | 42      | 42  | 42   | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 39  | 39   | 38   | 38   | 39  | 39  | 36   |
| oomcaa <sup>3</sup>       | 42      | 39  | 42   | 22  | 22  | 38  | 39  | 17  | 35  | 37  | 18  | 17  | 35  | 39   | 38   | 38   | 9   | 34  | 36   |
| mcaa <sup>4</sup>         | Y       | Y   | C    | A   | T   | W   | D   | D   | S   | L   | S   | G   | -   | -    | -    | -    | V   | V   | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 93% | 100% | 54% | 54% | 93% | 95% | 41% | 85% | 90% | 44% | 41% | 90% | 100% | 100% | 100% | 23% | 87% | 100% |
| pos occupied <sup>6</sup> | 1       | 3   | 1    | 5   | 3   | 2   | 2   | 8   | 3   | 5   | 8   | 6   | 5   | 1    | 1    | 1    | 10  | 6   | 1    |

Table 5A: Analysis of V lambda subgroup 1

| Framework III             |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
|---------------------------|------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|--|
| amino acid <sup>1</sup>   | 67   | 68  | 69  | 70   | 71  | 72  | 73   | 74  | 75  | 76  | 77   | 78  | 79  | 80  | 81  | 82  | 83   | 84  | 85  |  |
| A                         |      | 1   | 3   |      | 41  |     |      | 24  |     |     |      |     |     | 2   |     |     |      | 38  | 1   |  |
| B                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| C                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| D                         |      | 1   |     |      |     |     |      |     |     |     |      |     |     |     | 1   | 41  |      |     | 37  |  |
| E                         |      |     |     |      |     |     |      |     |     |     |      |     | 1   |     | 24  |     | 42   |     | 1   |  |
| F                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| G                         |      | 40  |     |      |     |     |      | 17  |     | 1   | 42   |     |     |     | 15  |     |      |     |     |  |
| H                         |      |     |     |      |     |     |      |     |     |     |      |     | 1   |     |     |     |      |     | 2   |  |
| I                         |      |     |     |      |     |     |      |     | 41  |     |      |     |     |     |     |     |      |     | 1   |  |
| K                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| L                         |      |     |     |      |     |     | 42   |     |     |     |      | 41  |     |     |     |     |      |     |     |  |
| M                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| N                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     | 1   |      |     |     |  |
| P                         |      |     |     |      |     |     |      |     |     |     |      |     |     | 2   |     |     |      |     |     |  |
| Q                         |      |     |     |      |     |     |      |     |     |     |      |     | 31  |     |     |     |      |     |     |  |
| R                         |      |     |     |      |     |     |      |     |     |     |      |     | 8   |     |     |     |      |     |     |  |
| S                         | 42   |     | 1   | 42   |     | 24  |      |     |     | 20  |      |     |     | 20  |     |     |      | 1   |     |  |
| T                         |      |     | 38  |      |     | 18  |      |     |     | 21  |      |     |     | 17  |     |     |      | 3   |     |  |
| V                         |      |     |     |      | 1   |     |      | 1   | 1   |     |      | 1   |     | 1   |     |     |      |     |     |  |
| W                         |      |     |     |      |     |     |      |     |     |     |      |     | 1   |     | 2   |     |      |     |     |  |
| X                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| Y                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| Z                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| -                         |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| unknown (?)               |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| not sequenced             |      |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |  |
| sum of seq <sup>2</sup>   | 42   | 42  | 42  | 42   | 42  | 42  | 42   | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42   | 42  | 42  |  |
| oomcaa <sup>3</sup>       | 42   | 40  | 38  | 42   | 41  | 24  | 42   | 24  | 41  | 21  | 42   | 41  | 31  | 20  | 24  | 41  | 42   | 38  | 37  |  |
| mcaa <sup>4</sup>         | S    | G   | T   | S    | A   | S   | L    | A   | I   | T   | G    | L   | Q   | S   | E   | D   | E    | A   | D   |  |
| rel. oomcaa <sup>5</sup>  | 100% | 95% | 90% | 100% | 98% | 57% | 100% | 57% | 98% | 50% | 100% | 98% | 74% | 48% | 57% | 98% | 100% | 90% | 88% |  |
| pos occupied <sup>6</sup> | 1    | 3   | 3   | 1    | 2   | 2   | 1    | 3   | 2   | 3   | 1    | 2   | 5   | 5   | 4   | 2   | 1    | 3   | 5   |  |

Table 5A: Analysis of V lambda subgroup 1

|                           | CDR II |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
|---------------------------|--------|-----|------|------|------|------|------|------|-----|-----|-----|------|-----|------|-----|------|-----|------|------|--|
| amino acid <sup>1</sup>   | 55     | 56  | A    | B    | C    | D    | E    | 57   | 58  | 59  | 60  | 61   | 62  | 63   | 64  | 65   | 66  | A    | B    |  |
| A                         | 1      |     |      |      |      |      |      |      |     |     |     |      |     |      | 5   |      |     |      |      |  |
| B                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| C                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| D                         |        |     |      |      |      |      |      |      |     |     | 38  |      |     |      |     |      |     |      |      |  |
| E                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| F                         |        |     |      |      |      |      |      |      |     |     |     |      | 38  |      |     |      |     |      |      |  |
| G                         |        |     |      |      |      |      |      | 41   |     |     | 2   |      |     |      | 36  |      |     |      |      |  |
| H                         |        |     |      |      |      |      |      |      |     |     | 1   |      |     |      |     |      |     |      |      |  |
| I                         |        |     |      |      |      |      |      |      | 17  |     |     |      | 3   |      |     |      |     |      |      |  |
| K                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      | 38  |      |      |  |
| L                         |        | 1   |      |      |      |      |      |      |     | 1   |     |      |     |      |     |      |     |      |      |  |
| M                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| N                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| P                         | 38     |     |      |      |      |      |      |      |     | 38  |     |      |     |      |     |      |     |      |      |  |
| Q                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| R                         |        |     |      |      |      |      |      |      |     |     |     | 42   |     |      |     |      | 4   |      |      |  |
| S                         | 2      | 40  |      |      |      |      |      |      |     | 2   |     |      |     | 42   |     | 42   |     |      |      |  |
| T                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      | 1   |      |     |      |      |  |
| V                         |        |     |      |      |      |      |      |      | 24  |     |     |      | 1   |      |     |      |     |      |      |  |
| W                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| X                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| Y                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| Z                         |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| -                         |        |     | 41   | 41   | 41   | 41   | 42   |      |     |     |     |      |     |      |     |      |     | 42   | 42   |  |
| unknown (?)               |        |     |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |
| not sequenced             | 1      | 1   |      |      |      |      |      | 1    | 1   | 1   | 1   |      |     |      |     |      |     |      |      |  |
| sum of seq <sup>2</sup>   | 41     | 41  | 41   | 41   | 41   | 41   | 42   | 41   | 41  | 41  | 41  | 42   | 42  | 42   | 42  | 42   | 42  | 42   | 42   |  |
| oomcaa <sup>3</sup>       | 38     | 40  | 41   | 41   | 41   | 41   | 42   | 41   | 24  | 38  | 38  | 42   | 38  | 42   | 36  | 42   | 38  | 42   | 42   |  |
| mcaa <sup>4</sup>         | P      | S   | -    | -    | -    | -    | -    | G    | V   | P   | D   | R    | F   | S    | G   | S    | K   | -    | -    |  |
| rel. oomcaa <sup>5</sup>  | 93%    | 98% | 100% | 100% | 100% | 100% | 100% | 100% | 59% | 93% | 93% | 100% | 90% | 100% | 86% | 100% | 90% | 100% | 100% |  |
| pos occupied <sup>6</sup> | 3      | 2   | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 3   | 3   | 1    | 3   | 1    | 3   | 1    | 2   | 1    | 1    |  |

Table 5A: Analysis of V lambda subgroup 1

|                           | Framework II |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
|---------------------------|--------------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|
| amino acid <sup>1</sup>   | 36           | 37  | 38  | 39  | 40   | 41  | 42  | 43  | 44   | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | 53  | 54  |  |  |  |  |  |
| A                         |              |     |     |     |      |     | 4   | 40  |      |     |     |     |     |     |     |     |     | 1   |     |  |  |  |  |  |
| B                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| C                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| D                         |              |     |     |     |      | 1   |     |     |      |     |     |     |     |     | 13  | 10  | 8   |     |     |  |  |  |  |  |
| E                         |              |     |     |     |      |     |     |     |      | 2   |     |     |     |     | 5   |     |     | 1   |     |  |  |  |  |  |
| F                         | 1            |     |     | 4   |      |     |     |     |      |     |     |     |     | 1   |     |     |     |     |     |  |  |  |  |  |
| G                         |              |     |     |     |      | 39  |     |     |      |     |     |     |     |     | 1   |     |     |     |     |  |  |  |  |  |
| H                         | 1            | 1   | 6   | 1   |      |     |     |     |      |     |     |     |     | 1   |     |     |     | 1   |     |  |  |  |  |  |
| I                         |              |     |     |     |      |     |     |     |      |     |     |     | 40  |     | 1   |     |     |     |     |  |  |  |  |  |
| K                         |              |     |     |     |      | 1   |     |     |      | 35  |     |     |     |     | 1   | 1   |     | 18  |     |  |  |  |  |  |
| L                         |              |     | 1   | 31  |      |     |     |     |      |     | 41  | 40  |     |     |     |     |     | 1   | 1   |  |  |  |  |  |
| M                         |              |     |     |     |      | 1   |     |     |      |     |     |     | 1   |     |     |     |     | 1   |     |  |  |  |  |  |
| N                         |              |     |     |     |      |     |     |     |      | 1   |     |     |     |     | 3   | 28  | 30  | 2   |     |  |  |  |  |  |
| P                         |              |     |     |     | 42   | 1   |     |     | 42   |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| Q                         |              | 39  | 34  |     |      |     |     |     |      |     |     |     |     |     |     |     |     | 15  |     |  |  |  |  |  |
| R                         |              | 2   |     | 1   |      | 1   |     |     |      | 4   |     |     |     |     | 7   |     |     | 2   | 40  |  |  |  |  |  |
| S                         |              |     |     |     |      |     |     | 1   |      |     |     |     |     |     | 9   | 2   | 3   | 1   |     |  |  |  |  |  |
| T                         |              |     |     |     |      |     | 36  | 1   |      |     |     |     |     |     | 1   |     |     |     |     |  |  |  |  |  |
| V                         |              |     | 1   | 5   |      |     |     |     |      |     | 1   | 2   | 1   |     |     |     |     |     |     |  |  |  |  |  |
| W                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |  |  |  |  |  |
| X                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| Y                         | 40           |     |     |     |      |     |     |     |      |     |     |     |     | 40  | 1   | 1   |     |     |     |  |  |  |  |  |
| Z                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| -                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| unknown (?)               |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| not sequenced             |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| sum of seq <sup>7</sup>   | 42           | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  |  |  |  |  |  |
| oomcaa <sup>1</sup>       | 40           | 39  | 34  | 31  | 42   | 39  | 36  | 40  | 42   | 35  | 41  | 40  | 40  | 40  | 13  | 28  | 30  | 18  | 40  |  |  |  |  |  |
| mcaa <sup>4</sup>         | Y            | Q   | Q   | L   | P    | G   | T   | A   | P    | K   | L   | L   | I   | Y   | D   | N   | N   | K   | R   |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 95%          | 93% | 81% | 74% | 100% | 93% | 86% | 95% | 100% | 83% | 98% | 95% | 95% | 95% | 31% | 67% | 71% | 43% | 95% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 3            | 3   | 4   | 5   | 1    | 4   | 4   | 3   | 1    | 4   | 2   | 2   | 3   | 3   | 10  | 5   | 4   | 9   | 3   |  |  |  |  |  |

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Table 5A: Analysis of V lambda subgroup 1

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|                           | CDRI |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
|---------------------------|------|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|--|
| amino acid <sup>1</sup>   | 20   | 21  | 22   | 23   | 24  | 25   | 26  | 27  | D   | E   | 28  | 29  | 30  | 31  | A   | 32  | 33  | 34  | 35   |  |  |
| A                         | 2    |     |      |      |     |      |     | 1   |     |     |     | 2   | 2   |     |     | 1   |     |     |      |  |  |
| B                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
| C                         |      |     |      | 42   |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
| D                         |      |     |      |      |     |      |     |     |     | 3   |     |     | 3   | 1   |     | 3   |     | 1   |      |  |  |
| E                         |      |     |      |      |     |      |     |     |     |     |     |     | 1   |     |     |     |     |     |      |  |  |
| F                         |      |     |      |      | 1   |      |     |     | 1   |     |     |     |     |     | 1   | 1   |     |     |      |  |  |
| G                         |      |     |      |      | 42  | 3    | 1   |     |     |     | 2   | 39  | 4   | 2   |     |     |     |     |      |  |  |
| H                         |      |     |      |      |     |      |     |     |     |     |     |     |     | 2   |     | 2   |     | 2   |      |  |  |
| I                         | 1    | 41  |      |      |     |      |     |     |     | 1   | 37  |     |     |     |     |     |     |     | 1    |  |  |
| K                         |      |     |      |      |     |      |     |     |     | 1   |     |     | 1   |     |     |     |     |     |      |  |  |
| L                         |      | 1   |      |      |     |      |     |     |     |     | 1   |     |     |     |     |     |     |     |      |  |  |
| M                         |      |     |      |      |     |      |     |     |     |     | 1   |     |     |     |     |     |     |     |      |  |  |
| N                         |      |     |      |      |     |      |     | 2   | 1   | 37  |     |     | 13  | 31  | 2   |     | 1   | 9   |      |  |  |
| P                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |     |      |  |  |
| Q                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |     |      |  |  |
| R                         |      |     |      |      |     |      | 1   | 1   |     |     |     |     | 5   |     |     |     |     |     |      |  |  |
| S                         | 1    |     | 42   |      | 38  | 34   | 34  | 38  |     |     |     |     | 13  | 1   | 1   | 3   |     | 19  |      |  |  |
| T                         | 38   |     |      |      | 3   | 4    | 3   | 2   |     |     |     | 1   |     | 1   |     | 7   |     | 2   |      |  |  |
| V                         |      |     |      |      |     |      |     |     |     |     | 1   |     |     |     |     | 2   | 40  |     |      |  |  |
| W                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     | 42   |  |  |
| X                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
| Y                         |      |     |      |      |     |      |     |     |     |     |     |     |     | 4   | 1   | 20  |     | 7   |      |  |  |
| Z                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
| -                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 36  |     |     |     |      |  |  |
| unknown (?)               |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |
| not sequenced             |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 1   | 1   | 1   | 1   |      |  |  |
| sum of seq <sup>2</sup>   | 42   | 42  | 42   | 42   | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 41  | 41  | 41  | 41  | 42   |  |  |
| oomcaa <sup>3</sup>       | 38   | 41  | 42   | 42   | 38  | 42   | 34  | 34  | 38  | 37  | 37  | 39  | 13  | 31  | 36  | 20  | 40  | 19  | 42   |  |  |
| mcaa <sup>4</sup>         | T    | I   | S    | C    | S   | G    | S   | S   | S   | N   | I   | G   | N   | N   | -   | Y   | V   | S   | W    |  |  |
| rel. oomcaa <sup>5</sup>  | 90%  | 98% | 100% | 100% | 90% | 100% | 81% | 81% | 90% | 88% | 88% | 93% | 31% | 74% | 88% | 49% | 98% | 46% | 100% |  |  |
| pos occupied <sup>6</sup> | 4    | 2   | 1    | 1    | 3   | 1    | 4   | 6   | 4   | 4   | 5   | 3   | 8   | 7   | 5   | 10  | 2   | 7   | 1    |  |  |



Table 5A: Analysis of V lambda subgroup 1

| amino acid <sup>1</sup>    | Framework I |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
|----------------------------|-------------|-----|-----|------|------|------|------|------|------|------|-----|------|-----|-----|-----|------|------|-----|------|
|                            | 1           | 2   | 3   | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11  | 12   | 13  | 14  | 15  | 16   | 17   | 18  | 19   |
| A                          |             |     |     |      |      |      |      |      |      |      | 19  |      | 18  | 20  |     |      |      |     |      |
| B                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| C                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| D                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| E                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 1   |      |
| F                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| G                          |             |     |     |      |      |      |      |      |      |      |     |      | 22  |     |     | 42   |      |     |      |
| H                          | 2           |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| I                          |             |     | 1   |      |      |      |      |      |      |      | 1   |      |     |     |     |      |      |     |      |
| K                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 14  |      |
| L                          |             |     | 1   | 41   |      |      |      |      |      |      | 1   |      |     |     |     |      |      |     |      |
| M                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| N                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| P                          |             |     |     |      |      |      | 41   | 41   |      |      |     |      |     | 1   | 41  |      |      |     |      |
| Q                          | 22          |     | 1   |      |      | 41   |      |      |      |      |     |      |     |     |     |      | 42   |     |      |
| R                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 25  |      |
| S                          |             | 39  |     |      |      |      |      |      | 41   |      |     | 41   |     |     | 1   |      |      | 1   |      |
| T                          |             |     |     |      | 41   |      |      |      |      |      |     |      |     | 19  |     |      |      | 1   |      |
| V                          |             | 1   | 38  |      |      |      |      |      |      |      | 20  |      | 1   | 1   |     |      |      |     | 42   |
| W                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| X                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| Y                          |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| Z                          | 16          |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| -                          |             |     |     |      |      |      |      |      |      | 41   |     |      |     |     |     |      |      |     |      |
| unknown (?)                |             |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| not sequenced <sup>6</sup> | 2           | 2   | 1   | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   | 1    | 1   | 1   | 1   |      |      |     |      |
| sum of seq <sup>7</sup>    | 40          | 40  | 41  | 41   | 41   | 41   | 41   | 41   | 41   | 41   | 41  | 41   | 41  | 41  | 42  | 42   | 42   | 42  | 42   |
| oomcaa <sup>1</sup>        | 22          | 39  | 38  | 41   | 41   | 41   | 41   | 41   | 41   | 41   | 20  | 41   | 22  | 20  | 41  | 42   | 42   | 25  | 42   |
| mcaa <sup>4</sup>          | Q           | S   | V   | L    | T    | Q    | P    | P    | S    | -    | V   | S    | G   | A   | P   | G    | Q    | R   | V    |
| rel. oomcaa <sup>5</sup>   | 55%         | 98% | 93% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 49% | 100% | 54% | 49% | 98% | 100% | 100% | 60% | 100% |
| pos occupied <sup>6</sup>  | 3           | 2   | 4   | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 4   | 1    | 3   | 4   | 2   | 1    | 1    | 5   | 1    |



Table 4D: Analysis of V kappa subgroup 4

|                           | Framework IV |      |      |     |      |     |     |     |     |     |      |     |      |     |
|---------------------------|--------------|------|------|-----|------|-----|-----|-----|-----|-----|------|-----|------|-----|
| amino acid <sup>1</sup>   | 97           | 98   | 99   | 100 | 101  | 102 | 103 | 104 | 105 | 106 | A    | 107 | 108  | sum |
| A                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 183 |
| B                         |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| C                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 68  |
| D                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 154 |
| E                         |              |      |      |     |      |     |     |     | 14  |     |      |     |      | 105 |
| F                         |              | 15   |      |     |      |     |     |     |     |     |      |     |      | 82  |
| G                         |              |      | 15   | 4   | 15   |     |     |     |     |     |      |     |      | 228 |
| H                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 6   |
| I                         |              |      |      |     |      |     |     |     |     | 14  |      |     |      | 135 |
| K                         |              |      |      |     |      |     | 14  |     |     |     |      | 13  |      | 158 |
| L                         |              |      |      |     |      |     |     | 4   |     |     |      |     |      | 258 |
| M                         | 1            |      |      |     |      |     |     |     |     |     |      |     |      | 27  |
| N                         |              |      |      |     |      |     |     |     |     |     |      | 1   |      | 136 |
| P                         |              |      |      |     |      | 1   |     |     |     |     |      |     |      | 195 |
| Q                         |              |      |      | 11  |      |     |     | 1   |     |     |      |     |      | 264 |
| R                         |              |      |      |     |      |     | 1   |     | 1   |     |      | 1   | 11   | 116 |
| S                         | 2            |      |      |     |      |     |     |     |     | 1   |      |     |      | 499 |
| T                         | 12           |      |      |     |      | 14  |     |     |     |     |      |     |      | 236 |
| V                         |              |      |      |     |      |     |     | 9   |     |     |      |     |      | 196 |
| W                         |              |      |      |     |      |     |     | 1   |     |     |      |     |      | 69  |
| X                         |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| Y                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 254 |
| -                         |              |      |      |     |      |     |     |     |     | 15  |      |     |      | 106 |
| unknown (?)               |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| not sequenced             | 18           | 18   | 18   | 18  | 18   | 18  | 18  | 18  | 18  | 18  | 18   | 18  | 22   | 518 |
| sum of seq <sup>1</sup>   | 15           | 15   | 15   | 15  | 15   | 15  | 15  | 15  | 15  | 15  | 15   | 15  | 11   |     |
| oomcaa <sup>1</sup>       | 12           | 15   | 15   | 11  | 15   | 14  | 14  | 9   | 14  | 14  | 15   | 13  | 11   |     |
| mcaa <sup>1</sup>         | T            | F    | G    | Q   | G    | T   | K   | V   | E   | I   | -    | K   | R    |     |
| rel. oomcaa <sup>1</sup>  | 80%          | 100% | 100% | 73% | 100% | 93% | 93% | 60% | 93% | 93% | 100% | 87% | 100% |     |
| pos occupied <sup>1</sup> | 3            | 1    | 1    | 2   | 1    | 2   | 2   | 4   | 2   | 2   | 1    | 3   | 1    |     |

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Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | CDR III |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
|---------------------------|---------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|-----|
|                           | 85      | 86   | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B    | C    | D    | E    | F    | 96  |
| A                         |         |      |     |      |     |     |     |     |     | 1   |     |     |      |      |      |      |      |     |
| B                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| C                         |         |      |     | 33   |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| D                         |         |      |     |      |     |     |     | 1   | 1   |     |     |     |      |      |      |      |      |     |
| E                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| F                         |         |      | 1   |      |     |     |     | 1   |     |     |     |     |      |      |      |      |      |     |
| G                         |         |      |     |      |     |     |     |     | 2   | 1   |     |     |      |      |      |      |      |     |
| H                         |         |      | 1   |      | 3   |     |     |     |     |     |     |     |      |      |      |      |      |     |
| I                         |         |      |     |      |     |     |     |     |     | 2   |     |     |      |      |      |      |      |     |
| K                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| L                         |         |      |     |      |     | 1   |     | 2   |     | 1   | 3   |     |      |      |      |      |      | 1   |
| M                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| N                         |         |      |     |      |     |     |     |     | 4   | 4   |     |     |      |      |      |      |      |     |
| P                         |         |      |     |      |     |     |     |     |     | 1   | 29  | 1   |      |      |      |      |      | 4   |
| Q                         |         |      |     |      | 30  | 32  |     |     |     |     | 1   |     |      |      |      |      |      | 1   |
| R                         |         |      |     |      |     |     |     |     | 1   |     |     | 1   |      |      |      |      |      | 2   |
| S                         |         |      |     |      |     |     | 2   |     | 23  | 2   |     |     |      |      |      |      |      | 1   |
| T                         |         |      |     |      |     |     |     |     | 2   | 22  |     |     |      |      |      |      |      |     |
| V                         | 33      |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| W                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      | 2   |
| X                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| Y                         |         | 33   | 31  |      |     |     | 31  | 29  |     |     |     |     |      |      |      |      |      | 1   |
| -                         |         |      |     |      |     |     |     |     |     |     |     | 13  | 15   | 15   | 15   | 15   | 15   | 3   |
| unknown (?)               |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |      |      |     |
| not sequenced             |         |      |     |      |     |     |     |     |     |     |     | 18  | 18   | 18   | 18   | 18   | 18   | 18  |
| sum of seq <sup>2</sup>   | 33      | 33   | 33  | 33   | 33  | 33  | 33  | 33  | 33  | 33  | 33  | 15  | 15   | 15   | 15   | 15   | 15   | 15  |
| oomcaa <sup>3</sup>       | 33      | 33   | 31  | 33   | 30  | 32  | 31  | 29  | 23  | 22  | 29  | 13  | 15   | 15   | 15   | 15   | 15   | 4   |
| mcaa <sup>4</sup>         | V       | Y    | Y   | C    | Q   | Q   | Y   | Y   | S   | T   | P   | -   | -    | -    | -    | -    | -    | P   |
| rel. oomcaa <sup>5</sup>  | 100%    | 100% | 94% | 100% | 91% | 97% | 94% | 88% | 70% | 67% | 88% | 87% | 100% | 100% | 100% | 100% | 100% | 27% |
| pos occupied <sup>6</sup> | 1       | 1    | 3   | 1    | 2   | 2   | 2   | 4   | 6   | 7   | 3   | 3   | 1    | 1    | 1    | 1    | 1    | 8   |

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Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework III |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
|---------------------------|---------------|------|------|-----|-----|------|------|------|------|-----|-----|-----|-----|------|------|------|------|-----|
|                           | 67            | 68   | 69   | 70  | 71  | 72   | 73   | 74   | 75   | 76  | 77  | 78  | 79  | 80   | 81   | 82   | 83   | 84  |
| A                         |               |      |      |     |     |      |      |      |      |     |     |     |     | 33   |      |      |      | 32  |
| B                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| C                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| D                         |               |      |      | 32  |     |      |      |      |      |     |     |     |     |      |      | 33   |      |     |
| E                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      | 33   |      |      |     |
| F                         |               |      |      |     | 32  |      |      |      |      |     |     |     |     |      |      |      |      |     |
| G                         |               | 33   |      | 1   |     |      |      |      |      |     |     |     |     |      |      |      |      | 1   |
| H                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| I                         |               |      |      |     |     |      |      |      | 33   |     |     |     |     |      |      |      |      |     |
| K                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| L                         |               |      |      |     |     |      | 33   |      |      |     |     | 32  |     |      |      |      |      |     |
| M                         |               |      |      |     |     |      |      |      |      |     |     |     | 1   |      |      |      |      |     |
| N                         |               |      |      |     |     |      |      |      |      | 2   | 1   |     |     |      |      |      |      |     |
| P                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| Q                         |               |      |      |     |     |      |      |      |      |     |     |     | 32  |      |      |      |      |     |
| R                         |               |      |      |     |     |      |      |      |      |     |     |     | 1   |      |      |      |      |     |
| S                         | 33            |      |      |     |     |      |      |      |      | 30  | 32  |     |     |      |      |      |      |     |
| T                         |               |      | 33   |     |     | 33   |      | 33   |      | 1   |     |     |     |      |      |      |      |     |
| V                         |               |      |      |     | 1   |      |      |      |      |     |     |     |     |      |      |      | 33   |     |
| W                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| X                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| Y                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| -                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| unknown (?)               |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| not sequenced             |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| sum of seq <sup>2</sup>   | 33            | 33   | 33   | 33  | 33  | 33   | 33   | 33   | 33   | 33  | 33  | 33  | 33  | 33   | 33   | 33   | 33   | 33  |
| oomcaa <sup>3</sup>       | 33            | 33   | 33   | 32  | 32  | 33   | 33   | 33   | 33   | 30  | 32  | 32  | 32  | 33   | 33   | 33   | 33   | 32  |
| mcaa <sup>4</sup>         | S             | G    | T    | D   | F   | T    | L    | T    | I    | S   | S   | L   | Q   | A    | E    | D    | V    | A   |
| rel. oomcaa <sup>5</sup>  | 100%          | 100% | 100% | 97% | 97% | 100% | 100% | 100% | 100% | 91% | 97% | 97% | 97% | 100% | 100% | 100% | 100% | 97% |
| pos occupied <sup>6</sup> | 1             | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 3   | 2   | 2   | 2   | 1    | 1    | 1    | 1    | 2   |

Table 4D: Analysis of V kappa subgroup 4

|                           | CDR II |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
|---------------------------|--------|------|-----|-----|-----|------|-----|------|------|------|------|------|-----|------|-----|------|------|------|
| amino acid <sup>1</sup>   | 49     | 50   | 51  | 52  | 53  | 54   | 55  | 56   | 57   | 58   | 59   | 60   | 61  | 62   | 63  | 64   | 65   | 66   |
| A                         |        |      | 30  |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| B                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| C                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| D                         |        |      |     |     |     |      |     |      |      |      |      | 33   |     |      |     |      |      |      |
| E                         |        |      |     |     |     |      | 32  |      |      |      |      |      |     |      |     |      |      |      |
| F                         |        |      |     |     |     |      |     |      |      |      |      |      |     | 33   |     |      |      |      |
| G                         |        |      |     |     |     |      |     |      | 33   |      |      |      |     |      | 1   | 33   |      | 33   |
| H                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| I                         |        |      |     |     | 1   |      |     |      |      |      |      |      |     |      |     |      |      |      |
| K                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| L                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| M                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| N                         |        |      |     |     | 2   |      |     |      |      |      |      |      |     |      |     |      |      |      |
| P                         |        |      |     | 1   |     |      |     |      |      |      | 33   |      | 1   |      |     |      |      |      |
| Q                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| R                         |        |      |     |     |     | 33   |     |      |      |      |      |      |     | 32   |     |      |      |      |
| S                         |        |      | 1   | 31  | 1   |      |     | 33   |      |      |      |      |     |      | 32  |      | 33   |      |
| T                         |        |      | 2   | 1   | 29  |      |     |      |      |      |      |      |     |      |     |      |      |      |
| V                         |        |      |     |     |     |      | 1   |      |      | 33   |      |      |     |      |     |      |      |      |
| W                         |        | 33   |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| X                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| Y                         | 33     |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| -                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| unknown (?)               |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| not sequenced             |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| sum of seq <sup>2</sup>   | 33     | 33   | 33  | 33  | 33  | 33   | 33  | 33   | 33   | 33   | 33   | 33   | 33  | 33   | 33  | 33   | 33   | 33   |
| oomcaa <sup>3</sup>       | 33     | 33   | 30  | 31  | 29  | 33   | 32  | 33   | 33   | 33   | 33   | 33   | 32  | 33   | 32  | 33   | 33   | 33   |
| mcaa <sup>4</sup>         | Y      | W    | A   | S   | T   | R    | E   | S    | G    | V    | P    | D    | R   | F    | S   | G    | S    | G    |
| rel. oomcaa <sup>5</sup>  | 100%   | 100% | 91% | 94% | 88% | 100% | 97% | 100% | 100% | 100% | 100% | 100% | 97% | 100% | 97% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 1      | 1    | 3   | 3   | 4   | 1    | 2   | 1    | 1    | 1    | 1    | 1    | 2   | 1    | 2   | 1    | 1    | 1    |

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Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework II |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
|---------------------------|--------------|------|------|-----|------|-----|-----|------|------|-----|-----|-----|-----|------|-----|-----|------|-----|
|                           | 31           | 32   | 33   | 34  | 35   | 36  | 37  | 38   | 39   | 40  | 41  | 42  | 43  | 44   | 45  | 46  | 47   | 48  |
| A                         |              |      |      | 32  |      |     |     |      |      | 2   |     |     |     |      |     |     |      |     |
| B                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| C                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| D                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| E                         |              |      |      |     |      |     |     |      |      |     | 1   |     |     |      |     |     |      |     |
| F                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| G                         |              |      |      |     |      |     |     |      |      |     | 32  |     |     |      |     |     |      |     |
| H                         |              |      |      |     |      | 2   |     |      |      |     |     |     |     |      |     |     |      |     |
| I                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      | 32  |
| K                         |              |      |      |     |      |     |     |      | 33   |     |     |     |     |      | 32  |     |      |     |
| L                         |              |      | 33   |     |      |     |     |      |      |     |     |     |     |      |     | 29  | 33   |     |
| M                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      | 1   |
| N                         | 33           |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| P                         |              |      |      |     |      |     |     |      |      | 31  |     |     | 31  | 33   |     |     |      |     |
| Q                         |              |      |      |     |      |     | 32  | 33   |      |     |     | 32  |     |      |     |     |      |     |
| R                         |              |      |      |     |      |     | 1   |      |      |     |     | 1   |     |      | 1   |     |      |     |
| S                         |              |      |      |     |      |     |     |      |      |     |     |     | 2   |      |     |     |      |     |
| T                         |              |      |      | 1   |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| V                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     | 4   |      |     |
| W                         |              |      |      |     | 33   |     |     |      |      |     |     |     |     |      |     |     |      |     |
| X                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| Y                         |              | 33   |      |     |      | 31  |     |      |      |     |     |     |     |      |     |     |      |     |
| -                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| unknown (?)               |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| not sequenced             |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| sum of seq <sup>2</sup>   | 33           | 33   | 33   | 33  | 33   | 33  | 33  | 33   | 33   | 33  | 33  | 33  | 33  | 33   | 33  | 33  | 33   | 33  |
| oomcaa <sup>3</sup>       | 33           | 33   | 33   | 32  | 33   | 31  | 32  | 33   | 33   | 31  | 32  | 32  | 31  | 33   | 32  | 29  | 33   | 32  |
| mcaa <sup>4</sup>         | N            | Y    | L    | A   | W    | Y   | Q   | Q    | K    | P   | G   | Q   | P   | P    | K   | L   | L    | I   |
| rel. oomcaa <sup>5</sup>  | 100%         | 100% | 100% | 97% | 100% | 94% | 97% | 100% | 100% | 94% | 97% | 97% | 94% | 100% | 97% | 88% | 100% | 97% |
| pos occupied <sup>6</sup> | 1            | 1    | 1    | 2   | 1    | 2   | 2   | 1    | 1    | 2   | 2   | 2   | 2   | 1    | 2   | 2   | 1    | 2   |

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Table 4D: Analysis of V kappa subgroup 4

|                           | CDRI |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
|---------------------------|------|------|------|------|------|------|-----|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | 19   | 20   | 21   | 22   | 23   | 24   | 25  | 26   | 27  | A    | B   | C   | D   | E   | F   | 28  | 29  | 30  |  |
| A                         | 26   |      |      |      |      |      | 1   |      |     |      | 1   |     |     |     |     |     |     |     |  |
| B                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| C                         |      |      |      |      | 33   |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| D                         |      |      |      |      |      |      |     |      |     |      | 1   |     | 1   |     |     | 1   |     |     |  |
| E                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| F                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| G                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| H                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| I                         |      |      | 26   |      |      |      |     |      |     |      | 1   |     |     |     |     |     |     |     |  |
| K                         |      |      |      |      |      | 33   |     |      |     |      |     |     |     |     |     | 2   |     | 30  |  |
| L                         |      |      |      |      |      |      |     |      |     |      | 2   | 31  |     |     |     |     |     |     |  |
| M                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| N                         |      |      |      | 26   |      |      |     |      |     |      |     |     |     |     |     | 30  | 31  | 1   |  |
| P                         |      |      |      |      |      |      | 1   |      |     |      |     |     |     |     | 1   |     |     |     |  |
| Q                         |      |      |      |      |      |      |     |      | 32  |      |     |     |     |     |     |     |     | 1   |  |
| R                         |      |      |      |      |      |      |     |      | 1   |      |     |     |     |     |     |     | 1   | 1   |  |
| S                         |      |      |      |      |      |      | 31  | 33   |     | 33   |     |     |     | 32  | 32  |     | 1   |     |  |
| T                         |      | 26   |      |      |      |      |     |      |     |      |     |     |     | 1   |     |     |     |     |  |
| V                         |      |      |      |      |      |      |     |      |     |      | 28  | 2   |     |     |     |     |     |     |  |
| W                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| X                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| Y                         |      |      |      |      |      |      |     |      |     |      |     |     | 32  |     |     |     |     |     |  |
| -                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| unknown (?)               |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| not sequenced             | 7    | 7    | 7    | 7    |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| sum of seq <sup>2</sup>   | 26   | 26   | 26   | 26   | 33   | 33   | 33  | 33   | 33  | 33   | 33  | 33  | 33  | 33  | 33  | 33  | 33  | 33  |  |
| oomcaa <sup>3</sup>       | 26   | 26   | 26   | 26   | 33   | 33   | 31  | 33   | 32  | 33   | 28  | 31  | 32  | 32  | 32  | 30  | 31  | 30  |  |
| mcaa <sup>4</sup>         | A    | T    | I    | N    | C    | K    | S   | S    | Q   | S    | V   | L   | Y   | S   | S   | N   | N   | K   |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 100% | 100% | 100% | 100% | 94% | 100% | 97% | 100% | 85% | 94% | 97% | 97% | 97% | 91% | 94% | 91% |  |
| pos occupied <sup>6</sup> | 1    | 1    | 1    | 1    | 1    | 1    | 3   | 1    | 2   | 1    | 5   | 2   | 2   | 2   | 2   | 3   | 3   | 4   |  |



Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework I |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
|---------------------------|-------------|------|-----|-----|------|-----|------|------|------|-----|------|-----|------|------|------|-----|-----|------|
|                           | 1           | 2    | 3   | 4   | 5    | 6   | 7    | 8    | 9    | 10  | 11   | 12  | 13   | 14   | 15   | 16  | 17  | 18   |
| A                         |             |      |     |     |      |     |      |      |      |     |      | 24  |      |      |      |     | 1   |      |
| B                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| C                         |             |      |     |     |      |     |      |      |      | 1   |      |     |      |      |      | 1   |     |      |
| D                         | 25          |      |     |     |      |     |      |      | 26   |     |      |     |      |      |      |     |     |      |
| E                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     | 25  |      |
| F                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| G                         |             |      |     |     |      |     |      |      |      |     |      | 1   |      |      |      | 24  |     |      |
| H                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| I                         |             | 26   |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| K                         |             |      |     |     |      | 1   |      |      |      |     |      |     |      |      |      |     |     |      |
| L                         |             |      |     | 1   |      |     |      |      |      | 26  |      |     |      |      | 26   |     |     |      |
| M                         |             |      |     | 24  |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| N                         | 1           |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| P                         |             |      |     |     |      |     |      | 26   |      |     |      | 1   |      |      |      |     |     |      |
| Q                         |             |      | 1   |     |      | 25  |      |      |      |     |      |     |      |      |      |     |     |      |
| R                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     | 26   |
| S                         |             |      |     |     |      |     | 26   |      |      | 25  |      |     |      | 26   |      | 1   |     |      |
| T                         |             |      |     |     | 26   |     |      |      |      |     |      |     |      |      |      |     |     |      |
| V                         |             |      | 25  | 1   |      |     |      |      |      |     |      |     | 26   |      |      |     |     |      |
| W                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| X                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| Y                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| -                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| unknown (?)               |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| not sequenced             | 7           | 7    | 7   | 7   | 7    | 7   | 7    | 7    | 7    | 7   | 7    | 7   | 7    | 7    | 7    | 7   | 7   | 7    |
| sum of seq <sup>2</sup>   | 26          | 26   | 26  | 26  | 26   | 26  | 26   | 26   | 26   | 26  | 26   | 26  | 26   | 26   | 26   | 26  | 26  | 26   |
| oomcaa <sup>3</sup>       | 25          | 26   | 25  | 24  | 26   | 25  | 26   | 26   | 26   | 25  | 26   | 24  | 26   | 26   | 26   | 24  | 25  | 26   |
| mcaa <sup>4</sup>         | D           | I    | V   | M   | T    | Q   | S    | P    | D    | S   | L    | A   | V    | S    | L    | G   | E   | R    |
| rel. oomcaa <sup>5</sup>  | 96%         | 100% | 96% | 92% | 100% | 96% | 100% | 100% | 100% | 96% | 100% | 92% | 100% | 100% | 100% | 92% | 96% | 100% |
| pos occupied <sup>6</sup> | 2           | 1    | 2   | 3   | 1    | 2   | 1    | 1    | 1    | 2   | 1    | 3   | 1    | 1    | 1    | 3   | 2   | 1    |

Table 4C: Analysis of V kappa subgroup 3

|                           | Framework IV |     |     |     |     |     |      |     |     |      |
|---------------------------|--------------|-----|-----|-----|-----|-----|------|-----|-----|------|
| amino acid <sup>1</sup>   | 101          | 102 | 103 | 104 | 105 | 106 | A    | 107 | 108 | sum  |
| A                         |              |     |     |     |     |     |      |     |     | 1345 |
| B                         |              |     |     |     |     |     |      |     |     | 2    |
| C                         |              |     |     |     |     |     |      |     |     | 375  |
| D                         |              |     |     |     | 23  |     |      |     |     | 564  |
| E                         |              |     | 3   |     | 141 |     |      |     |     | 759  |
| F                         |              |     |     |     |     | 6   |      |     |     | 765  |
| G                         | 166          |     |     |     |     |     |      |     | 1   | 1804 |
| H                         |              |     |     |     | 1   |     |      |     |     | 64   |
| I                         |              |     |     |     |     | 143 |      |     |     | 803  |
| K                         |              |     | 152 |     |     |     |      | 157 |     | 489  |
| L                         |              |     |     | 54  |     | 1   |      |     | 2   | 1596 |
| M                         |              |     |     |     |     | 3   |      |     |     | 36   |
| N                         |              | 1   |     |     |     |     |      | 3   |     | 255  |
| P                         |              | 1   |     | 1   |     |     |      |     |     | 1147 |
| Q                         |              |     | 1   |     | 1   |     |      |     |     | 1314 |
| R                         |              |     | 9   |     |     | 2   |      | 4   | 134 | 1326 |
| S                         |              | 2   |     |     |     |     |      |     |     | 2629 |
| T                         |              | 162 | 1   |     |     |     |      | 1   |     | 1593 |
| V                         |              |     |     | 111 |     | 11  |      |     |     | 646  |
| W                         |              |     |     |     |     |     |      |     |     | 287  |
| X                         |              |     |     |     |     |     |      |     |     |      |
| Y                         |              |     | 1   |     |     |     |      |     |     | 1014 |
| -                         | 1            | 1   | 1   | 1   | 1   | 1   | 166  | 1   | 1   | 2151 |
| unknown (?)               |              |     |     |     |     |     |      |     |     | 4    |
| not sequenced             | 16           | 16  | 15  | 16  | 16  | 16  | 17   | 17  | 45  | 337  |
| sum of seq <sup>2</sup>   | 167          | 167 | 168 | 167 | 167 | 167 | 166  | 166 | 138 |      |
| oomcaa <sup>3</sup>       | 166          | 162 | 152 | 111 | 141 | 143 | 166  | 157 | 134 |      |
| mcaa <sup>4</sup>         | G            | T   | K   | V   | E   | I   | -    | K   | R   |      |
| rel. oomcaa <sup>5</sup>  | 99%          | 97% | 90% | 66% | 84% | 86% | 100% | 95% | 97% |      |
| pos occupied <sup>6</sup> | 2            | 5   | 7   | 4   | 5   | 7   | 1    | 5   | 4   |      |

Table 4C: Analysis of V kappa subgroup 3

|                           | CDR III |     |     |     |     |     |     |      |      |      |      |     |     |     |     |     |  |  |  |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|------|------|------|------|-----|-----|-----|-----|-----|--|--|--|
| amino acid <sup>1</sup>   | 91      | 92  | 93  | 94  | 95  | A   | B   | C    | D    | E    | F    | 96  | 97  | 98  | 99  | 100 |  |  |  |
| A                         |         | 1   | 8   | 3   | 3   |     |     |      |      |      |      |     |     |     |     | 1   |  |  |  |
| B                         |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |     |  |  |  |
| C                         | 2       |     |     | 1   |     |     |     |      |      |      |      | 2   |     |     |     |     |  |  |  |
| D                         |         | 8   | 5   |     |     |     |     |      |      |      |      |     | 1   |     |     |     |  |  |  |
| E                         |         | 2   |     |     |     |     |     |      |      |      |      | 1   |     |     |     |     |  |  |  |
| F                         | 5       |     | 2   |     |     |     |     |      |      |      |      | 7   |     | 166 |     |     |  |  |  |
| G                         | 1       | 104 | 15  |     | 1   | 1   | 2   |      |      |      |      | 1   |     |     | 166 | 41  |  |  |  |
| H                         | 4       | 1   |     |     |     |     |     |      |      |      |      | 2   |     |     |     |     |  |  |  |
| I                         |         |     | 1   |     |     | 1   |     |      |      |      |      | 4   |     |     |     |     |  |  |  |
| K                         |         |     | 2   |     |     | 1   |     |      |      |      |      | 1   |     |     |     | 1   |  |  |  |
| L                         |         |     |     | 2   | 7   | 5   |     |      |      |      |      | 42  |     |     |     |     |  |  |  |
| M                         |         | 1   |     |     | 1   | 2   |     |      |      |      |      |     |     |     |     |     |  |  |  |
| N                         |         | 28  | 71  |     |     |     |     |      |      |      |      | 1   |     |     |     |     |  |  |  |
| P                         |         |     |     | 1   | 139 | 24  |     |      |      |      |      | 7   | 2   |     |     | 9   |  |  |  |
| Q                         | 1       |     | 1   |     | 3   | 1   |     |      |      |      |      | 3   |     |     |     | 114 |  |  |  |
| R                         | 34      | 2   | 3   |     | 2   | 2   |     |      |      |      |      | 19  |     |     |     |     |  |  |  |
| S                         | 2       | 33  | 58  | 102 | 15  | 2   |     |      |      |      |      | 1   | 8   |     |     |     |  |  |  |
| T                         |         | 2   | 13  | 1   | 1   | 2   |     |      |      |      |      | 1   | 154 |     |     |     |  |  |  |
| V                         |         |     |     |     | 3   | 1   |     |      |      |      |      | 2   |     |     |     |     |  |  |  |
| W                         |         |     |     | 69  |     |     |     |      |      |      |      | 24  |     |     |     |     |  |  |  |
| X                         |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |     |  |  |  |
| Y                         | 134     | 1   | 1   |     |     |     |     |      |      |      |      | 43  |     |     |     |     |  |  |  |
| -                         |         |     | 3   | 3   | 7   | 127 | 167 | 169  | 169  | 169  | 169  | 8   | 1   | 1   | 1   | 1   |  |  |  |
| unknown (?)               |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |     |  |  |  |
| not sequenced             |         |     |     |     |     | 14  | 14  | 14   | 14   | 14   | 14   | 14  | 17  | 16  | 16  | 16  |  |  |  |
| sum of seq <sup>2</sup>   | 183     | 183 | 183 | 182 | 182 | 169 | 169 | 169  | 169  | 169  | 169  | 169 | 166 | 167 | 167 | 167 |  |  |  |
| oomcaa <sup>3</sup>       | 134     | 104 | 71  | 102 | 139 | 127 | 167 | 169  | 169  | 169  | 169  | 43  | 154 | 166 | 166 | 114 |  |  |  |
| mcaa <sup>4</sup>         | Y       | G   | N   | S   | P   | -   | -   | -    | -    | -    | -    | Y   | T   | F   | G   | Q   |  |  |  |
| rel. oomcaa <sup>5</sup>  | 73%     | 57% | 39% | 56% | 76% | 75% | 99% | 100% | 100% | 100% | 100% | 25% | 93% | 99% | 99% | 68% |  |  |  |
| pos occupied <sup>6</sup> | 8       | 11  | 13  | 8   | 11  | 12  | 2   | 1    | 1    | 1    | 1    | 18  | 5   | 2   | 2   | 6   |  |  |  |

Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82  | 83  | 84  | 85  | 86  | 87  | 88  | 89  | 90  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| A                         |     |     |     |     |     |     | 3   |     |     | 174 |     |     |     |     |     |     |
| B                         |     |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |     |
| C                         |     |     |     |     |     |     |     |     | 2   |     |     |     | 1   | 182 |     |     |
| D                         |     |     | 1   |     |     |     | 3   | 182 |     |     |     |     |     |     |     |     |
| E                         |     |     |     |     | 149 |     | 175 |     |     |     |     |     |     |     |     | 2   |
| F                         |     | 1   |     |     |     |     |     |     | 178 |     | 2   | 1   | 4   |     |     |     |
| G                         |     |     | 3   |     |     |     |     | 1   |     | 2   |     |     |     |     |     |     |
| H                         |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     | 1   | 7   |
| I                         | 178 |     |     |     |     |     |     | 1   | 1   |     | 9   |     |     |     |     |     |
| K                         |     |     |     |     |     |     | 1   |     |     |     |     |     |     |     |     |     |
| L                         |     |     |     | 178 |     | 1   |     |     | 1   |     | 7   |     | 1   |     |     | 1   |
| M                         |     |     |     |     |     |     |     |     |     | 1   | 5   |     |     |     |     |     |
| N                         | 1   | 5   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| P                         |     |     |     |     |     | 149 |     |     |     |     |     |     |     |     |     |     |
| Q                         |     |     |     |     | 34  |     |     |     |     |     |     |     |     | 1   | 181 | 155 |
| R                         |     | 1   | 111 |     |     |     |     |     |     | 3   |     |     |     |     |     | 1   |
| S                         |     | 169 | 65  |     |     | 34  |     |     | 1   |     |     |     | 2   |     |     |     |
| T                         |     | 8   | 4   |     |     |     |     |     |     | 1   |     |     |     |     |     | 8   |
| V                         | 4   |     |     | 6   |     |     |     |     | 1   | 3   | 159 |     |     |     |     | 7   |
| W                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         | 1   |     |     |     |     |     |     |     |     |     | 1   | 183 | 176 |     | 1   | 2   |
| -                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| not sequenced             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 184 | 184 | 184 | 184 | 184 | 184 | 182 | 184 | 184 | 184 | 184 | 184 | 184 | 183 | 183 | 183 |
| oomcaa <sup>3</sup>       | 178 | 169 | 111 | 178 | 149 | 149 | 175 | 182 | 178 | 174 | 159 | 183 | 176 | 182 | 181 | 155 |
| mcaa <sup>4</sup>         | I   | S   | R   | L   | E   | P   | E   | D   | F   | A   | V   | Y   | Y   | C   | Q   | Q   |
| rel. oomcaa <sup>5</sup>  | 97% | 92% | 60% | 97% | 81% | 81% | 96% | 99% | 97% | 95% | 86% | 99% | 96% | 99% | 99% | 85% |
| pos occupied <sup>6</sup> | 4   | 5   | 5   | 2   | 3   | 3   | 4   | 3   | 6   | 6   | 7   | 2   | 5   | 2   | 3   | 8   |

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Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|
|                           | 59            | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67   | 68  | 69  | 70  | 71  | 72  | 73  | 74  |
| A                         |               | 68  |     |     |     |     |     | 3   |      | 5   | 3   | 1   |     | 3   |     |     |
| B                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| C                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| D                         |               | 112 |     |     |     | 1   |     |     |      |     |     | 152 |     |     |     |     |
| E                         |               |     |     |     |     |     |     | 1   |      | 1   |     | 30  |     |     |     |     |
| F                         |               |     |     | 183 |     |     |     |     |      |     |     |     | 183 |     | 2   |     |
| G                         |               |     |     |     |     | 184 | 3   | 178 | —    | 177 |     |     |     |     |     |     |
| H                         |               | 1   |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| I                         |               |     |     | 1   |     |     |     |     |      |     |     |     |     | 1   | 3   |     |
| K                         |               |     | 1   |     |     |     |     |     |      |     |     |     |     |     |     |     |
| L                         |               |     |     | 1   |     |     |     |     |      |     |     |     |     |     | 182 |     |
| M                         |               |     |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| N                         |               | 1   |     |     |     |     |     |     |      |     |     |     |     | 1   |     |     |
| P                         | 177           |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Q                         |               |     |     |     |     |     |     |     |      |     |     | 1   |     |     |     |     |
| R                         |               |     | 182 |     | 2   |     | 1   |     |      |     | 2   |     |     |     |     |     |
| S                         | 7             |     |     |     | 180 |     | 179 |     | 185  |     | 3   |     |     | 7   |     | 2   |
| T                         | 1             |     | 2   |     | 3   |     | 2   |     |      |     | 177 |     |     | 172 |     | 179 |
| V                         |               | 3   |     |     |     |     |     | 1   |      | 1   |     |     |     |     |     |     |
| W                         |               |     |     |     |     |     |     |     |      | 1   |     |     |     |     |     |     |
| X                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Y                         |               |     |     |     |     |     |     |     |      |     |     |     | 1   |     |     |     |
| -                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| unknown (?)               |               |     |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| not sequenced             |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 185           | 185 | 185 | 185 | 185 | 185 | 185 | 185 | 185  | 185 | 185 | 184 | 184 | 184 | 184 | 184 |
| oomcaa <sup>3</sup>       | 177           | 112 | 182 | 183 | 180 | 184 | 179 | 178 | 185  | 177 | 177 | 152 | 183 | 172 | 182 | 179 |
| mcaa <sup>4</sup>         | P             | D   | R   | F   | S   | G   | S   | G   | S    | G   | T   | D   | F   | T   | L   | T   |
| rel. oomcaa <sup>5</sup>  | 96%           | 61% | 98% | 99% | 97% | 99% | 97% | 96% | 100% | 96% | 96% | 83% | 99% | 93% | 99% | 97% |
| pos occupied <sup>6</sup> | 3             | 5   | 3   | 3   | 3   | 2   | 4   | 5   | 1    | 5   | 4   | 4   | 2   | 5   | 2   | 3   |

Table 4C: Analysis of V kappa subgroup 3

|                           | CDR II |     |     |     |     |     |     |     | CDR II |     |     |     |     |     |     |     |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|--------|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 43     | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51     | 52  | 53  | 54  | 55  | 56  | 57  | 58  |
| A                         | 176    |     |     |     |     |     |     | 4   | 147    |     |     |     | 176 | 1   |     |     |
| B                         |        |     |     |     |     |     |     |     |        |     |     |     |     |     |     |     |
| C                         |        |     |     |     |     |     |     |     | 1      |     |     |     |     |     |     |     |
| D                         |        |     |     |     |     |     |     | 43  |        |     |     |     | 2   |     | 4   |     |
| E                         |        |     |     |     |     |     |     |     |        |     |     |     |     |     |     |     |
| F                         |        |     |     | 1   |     | 1   | 4   |     |        |     |     |     |     |     |     |     |
| G                         |        |     |     |     |     |     |     | 125 |        |     |     |     | 2   | 10  | 179 |     |
| H                         |        |     |     |     |     |     | 9   |     | 1      |     |     |     |     |     |     |     |
| I                         |        |     |     |     |     | 178 |     |     |        |     |     |     |     | 1   |     | 168 |
| K                         |        |     | 1   |     |     |     |     |     |        |     | 7   | 1   |     |     |     |     |
| L                         |        | 1   |     | 179 | 174 | 1   |     |     |        |     |     |     |     |     |     |     |
| M                         |        |     |     |     |     | 3   |     |     |        |     | 1   |     |     |     |     |     |
| N                         |        |     | 1   |     |     |     |     | 1   |        |     | 53  |     |     | 2   |     |     |
| P                         | 5      | 184 |     |     |     |     |     |     |        | 2   |     |     | 2   | 2   |     |     |
| Q                         |        |     |     |     |     |     | 1   |     |        |     |     |     |     |     |     |     |
| R                         |        |     | 182 |     |     |     |     | 1   |        |     | 4   | 180 |     |     |     |     |
| S                         |        |     |     |     |     |     | 3   | 6   | 4      | 179 | 74  | 1   |     | 5   |     |     |
| T                         | 3      |     |     |     |     |     |     |     | 11     | 2   | 44  |     |     | 164 |     | 2   |
| V                         |        |     |     | 3   | 9   |     |     | 3   | 19     |     |     |     | 3   |     |     | 15  |
| W                         |        |     |     |     |     |     | 1   |     |        |     |     | 1   |     |     |     |     |
| X                         |        |     |     |     |     |     |     |     |        |     |     |     |     |     |     |     |
| Y                         |        |     |     |     |     |     | 165 |     |        |     |     |     |     |     | 2   |     |
| -                         |        |     |     |     |     |     |     |     |        |     |     |     |     |     |     |     |
| unknown (?)               |        |     | 1   |     |     |     |     |     |        |     |     |     |     |     |     |     |
| not sequenced             |        |     |     |     |     |     |     |     |        |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 184    | 185 | 185 | 183 | 183 | 183 | 183 | 183 | 183    | 183 | 183 | 183 | 185 | 185 | 185 | 185 |
| oomcaa <sup>3</sup>       | 176    | 184 | 182 | 179 | 174 | 178 | 165 | 125 | 147    | 179 | 74  | 180 | 176 | 164 | 179 | 168 |
| mcaa <sup>4</sup>         | A      | P   | R   | L   | L   | I   | Y   | G   | A      | S   | S   | R   | A   | T   | G   | I   |
| rel. oomcaa <sup>5</sup>  | 96%    | 99% | 98% | 98% | 95% | 97% | 90% | 68% | 80%    | 98% | 40% | 98% | 95% | 89% | 97% | 91% |
| pos occupied <sup>6</sup> | 3      | 2   | 3   | 3   | 2   | 4   | 6   | 7   | 6      | 3   | 6   | 4   | 5   | 7   | 3   | 3   |

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Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | Frame wo |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
|---------------------------|----------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|
|                           | F        | 28  | 29  | 30  | 31  | 32  | 33  | 34  | 35   | 36  | 37  | 38  | 39  | 40  | 41   | 42  |
| A                         |          |     |     | 1   | 1   |     |     | 181 |      |     |     |     |     |     |      |     |
| B                         |          |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| C                         |          |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| D                         |          |     | 1   | 1   | 2   | 1   |     |     |      |     |     |     |     |     |      |     |
| E                         |          |     |     |     |     | 1   |     |     |      |     |     |     | 1   |     |      | 1   |
| F                         |          | 1   |     |     |     | 7   |     |     |      | 1   |     |     |     |     |      |     |
| G                         |          |     | 2   | 7   | 3   | 1   |     | 2   |      |     |     |     |     | 1   | 184  |     |
| H                         |          |     | 1   |     |     | 2   |     |     |      | 1   |     | 12  | 1   | 1   |      |     |
| I                         |          | 24  | 4   | 1   | 1   |     |     |     |      |     |     |     |     |     |      |     |
| K                         |          |     |     | 1   | 1   |     |     |     |      |     |     |     | 153 |     |      |     |
| L                         |          | 8   | 1   |     |     | 1   | 176 |     |      |     |     | 3   |     |     |      | 2   |
| M                         |          |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| N                         |          |     | 3   | 12  | 25  | 32  |     |     |      |     |     |     |     |     |      |     |
| P                         |          |     |     |     | 1   |     |     |     |      |     |     |     |     | 170 |      |     |
| Q                         |          |     |     |     | 1   | 1   |     |     |      |     | 183 | 167 | 1   |     |      | 181 |
| R                         |          |     | 10  | 3   | 18  | 16  |     | 1   |      |     | 1   |     | 27  | 5   |      |     |
| S                         |          | 72  | 86  | 151 | 118 | 4   |     |     |      |     |     |     |     | 5   |      |     |
| T                         |          | 1   | 1   | 3   | 8   | 1   |     |     |      |     |     |     | 1   |     |      |     |
| V                         |          | 76  | 68  |     | 1   |     | 7   |     |      |     |     | 3   |     | 2   |      |     |
| W                         |          |     | 5   |     |     |     |     | 185 |      |     |     |     |     |     |      |     |
| X                         |          |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| Y                         |          |     |     | 1   | 1   | 115 |     |     | 183  |     |     |     |     |     |      |     |
| -                         | 182      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| unknown (?)               |          |     |     |     |     |     |     |     |      |     | 1   |     |     |     |      |     |
| not sequenced             |          |     |     |     |     |     |     |     |      |     |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 182      | 182 | 182 | 181 | 181 | 182 | 183 | 184 | 185  | 185 | 185 | 185 | 184 | 184 | 184  | 184 |
| oomcaa <sup>3</sup>       | 182      | 76  | 86  | 151 | 118 | 115 | 176 | 181 | 185  | 183 | 183 | 167 | 153 | 170 | 184  | 181 |
| mcaa <sup>4</sup>         | -        | V   | S   | S   | S   | Y   | L   | A   | W    | Y   | Q   | Q   | K   | P   | G    | Q   |
| rel. oomcaa <sup>5</sup>  | 100%     | 42% | 47% | 83% | 65% | 63% | 96% | 98% | 100% | 99% | 99% | 90% | 83% | 92% | 100% | 98% |
| pos occupied <sup>6</sup> | 1        | 6   | 11  | 10  | 13  | 12  | 2   | 3   | 1    | 3   | 2   | 4   | 6   | 6   | 1    | 3   |

Figure 4C: V lambda 3 (Vλ3) gene sequence

|            |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|------------|------------|---|---|---|---|---|---|---|---|---|---|---|---|
| S          | Y          | E          | L          | T          | Q | P | P | S | V | S | V | A | P | G | Q | T |
| SexAI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| AGCTATGAAC | TGACCCAGCC | GCCTTCAGTG | AGCGTTGCAC | CAGGTCAGAC |   |   |   |   |   |   |   |   |   |   |   |   |
| TCGATACTTG | ACTGGGTCGG | CGGAAGTCAC | TCGCAACGTG | GTCCAGTCTG |   |   |   |   |   |   |   |   |   |   |   |   |
| Eco57I     |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| A          | R          | I          | S          | C          | S | G | D | A | L | G | D | K | Y | A | S |   |
| BssSI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| CGCGCGTATC | TCGTGTAGCG | GGATGCGCT  | GGGCGATAAA | TACGCGAGCT |   |   |   |   |   |   |   |   |   |   |   |   |
| GCGCGCATAG | AGCACATCGC | CGCTACGCCA | CCCGCTATTT | ATGCGCTCGA |   |   |   |   |   |   |   |   |   |   |   |   |
| W          | Y          | Q          | Q          | K          | P | G | Q | A | P | V | L | V | I | Y | D | D |
| KpnI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| XmaI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| GGTACCAGCA | GAAACCCGGG | CAGGCGCCAG | TTCTGGTGAT | TTATGATGAT |   |   |   |   |   |   |   |   |   |   |   |   |
| CCATGGTCGT | CTTTGGGCCC | GTCCGCGGTC | AAGACCACTA | AATACTACTA |   |   |   |   |   |   |   |   |   |   |   |   |
| BbeI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |

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Figure 4C: V lambda 3 (A3) gene sequence (continued)

|                                                                                                                                                                                                                                                   |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------|-------------|------------|---|---|---|---|---|---|---|---|---|---|---|---|
| S                                                                                                                                                                                                                                                 | D          | R          | P           | S          | G | I | P | E | R | F | S | G | S | N | S | G |
| <div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <p>Bsu36I</p> <p>~~~~~</p> </div> <div style="text-align: center;"> <p>BamHI</p> <p>~~~~~</p> </div> </div>                   |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |   |
| TCTGACCGTC                                                                                                                                                                                                                                        | CCTCAGGCAT | CCCGGAACGC | TTAGCCGGAT  | CCAACAGCGG |   |   |   |   |   |   |   |   |   |   |   |   |
| AGACTGGCAG                                                                                                                                                                                                                                        | GGAGTCCGTA | GGCCCTTGCG | AAATCGCCTA  | GGTTGTCGCC |   |   |   |   |   |   |   |   |   |   |   |   |
| <div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <p>N T A T L T I S G T Q A E D E A</p> <p>BbsI</p> <p>~~~~~</p> </div> </div>                                                 |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |   |
| CAACACCGCG                                                                                                                                                                                                                                        | ACCTGACCA  | TTAGCGGCAC | TCAGGCGGAA  | GACGAAGCGG |   |   |   |   |   |   |   |   |   |   |   |   |
| GTTGTGGCGC                                                                                                                                                                                                                                        | TGGGACTGGT | AATCGCCGTG | AGTCCGCCCTT | CTGCTTCGCC |   |   |   |   |   |   |   |   |   |   |   |   |
| D Y Y C                                                                                                                                                                                                                                           | Q Q H      | Y T P      | P V F       | G G G      |   |   |   |   |   |   |   |   |   |   |   |   |
| ATTATTATTG                                                                                                                                                                                                                                        | CCAGCAGCAT | TATACCACCC | CGCCTGTGTT  | TGGCGGCGGC |   |   |   |   |   |   |   |   |   |   |   |   |
| TAATAATAAC                                                                                                                                                                                                                                        | GGTCGTCGTA | ATATGGTGGG | GCGGACACAA  | ACCGCCGCCG |   |   |   |   |   |   |   |   |   |   |   |   |
| <div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <p>T K L T V L G</p> <p>HpaI</p> <p>~~~~~</p> </div> <div style="text-align: center;"> <p>MscI</p> <p>~~~~~</p> </div> </div> |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ACGAAGTTAA                                                                                                                                                                                                                                        | CCGTTCTTGG | C          |             |            |   |   |   |   |   |   |   |   |   |   |   |   |
| TGCTTCAATT                                                                                                                                                                                                                                        | GGCAAGAACC | G          |             |            |   |   |   |   |   |   |   |   |   |   |   |   |

Figure 5A: V heavy chain 1A (VH1A) gene sequence

```

Q V Q L V Q S G A E V K K P G S S
MfeI
~~~~~
CAGGTGCAAT TGGTTCAGTC TGGCGCGGAA GTGAAAAAAC CGGGCAGCAG
GTCCACGTTA ACCAAGTCAG ACCGCGCCTT CACTTTTTCG GCCCGTCGTC

V  K  V  S  C  K  A  S  G  G  T  F  S  S  Y  A
BspEI
~~~~~
CGTGAAAGTG AGCTGCAAAG CCTCCGGAGG CACTTTTAGC AGCTATGCCA
GCACTTTCAC TCGACGTTTC GGAGGCCTCC GTGAAAAATCG TCGATACGCT

I S W V R Q A P G Q G L E W M G G
BstXI
~~~~~
TTAGCTGGGT GCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCGGC
AATCGACCCA CGCGGTTTCG GGACCCGTCC CAGAGCTCAC CTACCCGCCC

I  I  P  I  F  G  T  A  N  Y  A  Q  K  F  Q  G  R
ATTATTCCGA TTTTGGCAC GCGGAACCTAC GCGCAGAAAGT TTCAGGGCCG
TAATAAGGCT AAAAACCGTG CCGCTTGATG CCGGTCTTCA AAGTCCCGGC

V  T  I  T  A  D  E  S  T  S  T  A  Y  M  E  L
BstEII

```

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Figure 5A: V heavy chain 1A (VH1A) gene sequence (continued)

```

~~~~~
GGTGACCATT ACCGCGGATG AAAGCACCAG CACCGCGTAT ATGGAAGTGA
CCACTGGTAA TGGCGCCTAC TTTCGTGGTC GTGGCGCATA TACCTTGACT

S S L R S E D T A V Y Y C A R W G
 EagI BssHII
          ~~~~~
GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGCG
CGTCGGACGC ATCGCTTCTA TGCCGGCACA TAATAACGCG CGCAACCCCG

G D G F Y A M D Y W G Q G T L V T
          StyI
          ~~~~~
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

V S S
 BlnI
      ~~~~~
GGTAGCTCA G
CCAATCGAGT C

```

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Figure 5B: V heavy chain 1B (VH1B) gene sequence

```

Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S
      MfeI
-----
CAGGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGGCGCGAG
GTCCACGTTA ACCAAGTCTC GCCGCGCCTT CACTTTTGTG GCCCGCGCTC

V  K  V  S  C  K  A  S  G  Y  T  F  T  S  Y  Y
      BspEI
-----
CGTGAAAGTG AGCTGCAAAG CCTCCGGATA TACCTTTACC AGCTATTATA
GCACTTTCAC TCGACGTTTC GGAGGCCTAT ATGGAAATGG TCGATAATAT

M  H  W  V  R  Q  A  P  G  Q  G  L  E  W  M  G  W
      BstXI
      XhoI
-----
TGCACTGGGT CCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCTGG
ACGTGACCCA GCGGTTTCGG GGACCCGTCC CAGAGCTCAC CTACCCGACC

I  N  P  N  S  G  G  T  N  Y  A  Q  K  F  Q  G  R
ATTAACCCGA ATAGCGGCGG CACGAACACTAC GCGCAGAAGT TTCAGGGCCG
TAATTGGGCT TATCGCCGCC GTGCTTGATG CGCGTCTCA AAGTCCCGGC

```

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Figure 5B: V heavy chain 1B (VH1B) gene sequence (continued)

```

V   T   M   T   R   D   T   S   I   S   T   A   Y   M   E   L
BstEII
-----
GGTGACCATG ACCCGTGATA CCAGCATTAG CACCGCGTAT ATGGAAGTGA
CCACTGGTAC TGGGCACTAT GTCGTAATC GTGGCGCATA TACCTTGACT

S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   W   G
EagI
-----
GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGGC
CGTCGGACGC ATCGCTTCTA TGCCGGCACA TAATAACGCG CGCAACCCCG

G   D   G   F   Y   A   M   D   Y   W   G   Q   G   T   L   V   T
StyI
-----
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

V   S   S
B1pI
-----
GGTAGCTCA G
CCAATCGAGT C

```

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Figure 5C: V heavy chain 2 (VH2) gene sequence

```

Q V Q L K E S G P A L V K P T Q T
MfeI
~~~~~
CAGGTGCAAT TGAAGAAG CCGCCCGGCC CTGTTGAAAC CGACCAAAC
GTCCACGTA ACTTCTTC GCCGGCCGG GACCACTTG GCTGGGTTTG

L T L T C T F S G F S L S T S G
BspEI
~~~~~
CCTGACCCCTG ACCTGTACCT TTTCCGGATT TAGCCTGTCC ACGTCTGGCG
GGACTGGGAC TGGACATGGA AAAGGCCTAA ATCGGACAGG TGCAGACCCG

V G V G W I R Q P P G K A L E W L
BstXI
~~~~~
XhoI
~~~~~
TTGGCGTGGG CTGGATTCGC CAGCCGCCCTG GAAAGCCCT CGAGTGGCTG
AACCGCACCC GACCTAAGCG GTCGGCGGAC CCTTTCGGGA GCTCACCGAC

A L I D W D D D K Y Y S T S L K T
MluI
~~~~~
GCTCTGATTG ATTGGGATGA TGATAAGTAT TATAGCACCA GCCTGAAAAC
CGAGACTAAC TAACCCCTACT ACTATTCTATA ATATCGTGGT CGGACTTTTG

```

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Figure 5C: V heavy chain 2 (VH2) gene sequence (continued)

```

R L T I S K D T S K N Q V V L T
MluI -----
 NspV

GCGTCTGACC ATTAGCAAAG ATACTTCGAA AAATCAGGTG GTGCTGACTA
CGCAGACTGG TAATCGTTTC TATGAAGCTT TTAGTCCAC CACGACTGAT

M T N M D P V D T A T Y Y C A R W
 BssHII

TGACCAACAT GGACCCGGTG GATACGGCCA CCTATTATTG CGCGCGTTGG
ACTGGTTGTA CTTGGGCCAC CTATGCCGGT GGATAATAAC GCGCGCAACC

G G D G F Y A M D Y W G Q G T L V
 StyI

GGCGGCGATG GCTTTTATGC GATGGATTAT TGGGGCCAAG GCACCCCTGGT
CCGCCGCTAC CGAAATACG CTACCTAATA ACCCCGGTTC CGTGGGACCA

T V S S
 BlnI

GACGGTAGC TCAG
CTGCCAATCG AGTC

```

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Figure 5D: V heavy chain 3 (VH3) gene sequence

```

E V Q L V E S G G G L V Q P G G S
MfeI
~~~~~
GAAGTGCAAT TGGTGGAAG CGGCGGCGGC CTGGTGCAAC CGGGCGGCAG
CTTCACGTTA ACCACCTTC GCCGCCGCCG GACCACGTTG GCCCGCCGTC

L R L S C A A S G F T F S S Y A
BspEI
~~~~~
CCTGCGTCTG AGTGCGCGG CCTCCGGATT TACCTTTAGC AGCTATGCCA
GGACGCAGAC TCGACGCGCC GGAGGCCTAA ATGGAATCG TCGATACGCT

M S W V R Q A P G K G L E W V S A
BstXI
~~~~~
XhoI
~~~~~
TGAGCTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCGCG
ACTCGACCCA CGCGGTTCCG GACCCCTCC CAGAGCTCAC CCACTCGCGC

I S G S G G S T Y Y A D S V K G R
ATTAGCGGTA GCGCGGCGCAG CACCTATTAT GCGGATAGCG TGAAGGCCG
TAATCGCCAT CGCCGCCGTC GTGGATAATA CGCTATCGC ACTTCCGCG

```

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|             |   |   |   |            |   |            |   |             |   |             |   |   |   |   |   |
|-------------|---|---|---|------------|---|------------|---|-------------|---|-------------|---|---|---|---|---|
| F           | T | I | S | R          | D | N          | S | K           | N | T           | L | Y | L | Q | M |
|             |   |   |   | PmlI       |   |            |   | NspV        |   |             |   |   |   |   |   |
| TTTTACCATT  |   |   |   | TCACGTGATA |   | ATTCGAAAAA |   | CACCCCTGTAT |   | CTGCAAAATGA |   |   |   |   |   |
| AAAAATGGTAA |   |   |   | AGTGCACTAT |   | TAAGCTTTTT |   | GTGGGACATA  |   | GACGTTTACT  |   |   |   |   |   |
| N           | S | L | R | A          | E | D          | T | A           | V | Y           | C | A | R | W | G |
|             |   |   |   |            |   | EagI       |   |             |   | BssHII      |   |   |   |   |   |
| ACAGCCTGCG  |   |   |   | TGCGGAAGAT |   | ACGGCCGTGT |   | ATTATTGCGC  |   | GCGTTGGGGC  |   |   |   |   |   |
| TGTCGGACGC  |   |   |   | ACGCCTTCTA |   | TGCCGGCACA |   | TAATAACGCG  |   | CGCAACCCCG  |   |   |   |   |   |
| G           | D | G | F | Y          | A | M          | D | Y           | W | G           | Q | G | T | L | V |
|             |   |   |   |            |   |            |   |             |   | StyI        |   |   |   |   |   |
| GGCGATGGCT  |   |   |   | TTTATGCGAT |   | GGATTATTGG |   | GGCCAAGGCA  |   | CCCTGGTGAC  |   |   |   |   |   |
| CCGCTACCGA  |   |   |   | AAATACGCTA |   | CCTAATAACC |   | CCGGTTCCGT  |   | GGGACCACCTG |   |   |   |   |   |
| V           | S | S |   |            |   |            |   |             |   |             |   |   |   |   |   |
|             |   |   |   | B1pI       |   |            |   |             |   |             |   |   |   |   |   |
| GGTTAGCTCA  |   |   |   | G          |   |            |   |             |   |             |   |   |   |   |   |
| CCCAATCGAGT |   |   |   | C          |   |            |   |             |   |             |   |   |   |   |   |

Figure 5E: V heavy chain 4 (VH4) gene sequence

```

Q V Q L Q E S G P G L V K P S E T
 MfeI

CAGGTGCAAT TGCAAGAAAG TGGTCCGGGC CTGGTGAAAC CGAGCGAAAC
GTCCACGTTA ACGTTCTTC ACCAGGCCCG GACCACTTG GCTCGCTTG

L S L T C T V S G G S I S S Y Y
 BspEI

CCTGAGCCTG ACCTGCACCG TTTCCGGAGG CAGCATTAGC AGCTATTATT
GGA CTGGAC TGGACGTGGC AAAGCCTCC GTCGTAATCG TCGATAATAA

W S W I R Q P P G K G L E W I G Y
 BstXI

GGAGCTGGAT TCGCCAGCCG CCTGGGAAGG GTCTCGAGTG GATTGGCTAT
CCTCGACCTA AGCGGTCGGC GGACCCCTCC CAGAGCTCAC CTAACCGATA

I Y Y S G S T N Y N P S L K S R V
 BstEII

ATTATTATA GCGGCAGCAC CAACTATAAT CCGAGCCTGA AAAGCCGGGT
TAAATAATAT CGCCGTCGTG GTTGATATTA GGCTCGGACT TTTCGGCCCA

```

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Figure 5E: V heavy chain 4 (VH4) gene sequence (continued)

```

T I S V D T S K N Q F S L K L S
BstEII

NspV

GACCATTAGC GTTGATACTT CGAAAAACCA GTTAGCCTG AAAC TGAGCA
CTGGTAATCG CAACTATGAA GCTTTTGGT CAAATCGGAC TTTGACTCGT

S V T A A D T A V Y Y C A R W G G
EagI

BssHII

CGGTGACGGC GCGGATACG GCCGTGTATT ATTGCGCGCG TTGGGGCGGC
CGCACTGCCG CCGCCTATGC CGGCACATAA TAACGCGCGC AACCCGCCG

D G F Y A M D Y W G Q G T L V T V
StyI

GATGGCTTTT ATGCGATGGA TTATTGGGGC CAAGGCACCC TGGTGACGGT
CTACCGAAAA TACGCTACCT AATAACCCCG GTTCCGTGGG ACCACTGCCA

S S
B1pI

TAGCTCAG
ATCGAGTC

```

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Figure 5F: V heavy chain 5 (VH5) gene sequence

```

E V Q L V Q S G A E V K K P G E S
 MfeI
~~~~~
GAAGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGCGGAAAG
CTTCACGTTA ACCAAGTCTC GCCGCGCCTT CACTTTTTCG GCCCGCTTTC

      L  K  I  S  C  K  G  S  G  Y  S  F  T  S  Y  W
                        BspEI
                        ~~~~~
CCTGAAAATT AGCTGCAAAG GTTCCGGATA TTCTTTTACG AGCTATTGGA
GGACTTTTAA TCGACGTTTC CAAGGCCTAT AAGGAAATGC TCGATAACCT

 I G W V R Q M P G K G L E W M G I
 BstXI
                        ~~~~~
                        XhoI
                        ~~~~~
TTGGCTGGGT GCGCCAGATG CCTGGGAAGG GTCTCGAGTG GATGGGCATT
AACCGACCCA CGCGGTCTAC GGACCCTTCC CAGAGCTCAC CTACCCGTAA

 I Y P G D S D T R Y S P S F Q G Q
ATTATCCGG GCGATAGCGA TACCCGTTAT TCTCCGAGCT TTCAGGGCCA
TAAATAGGCC CGCTATCGCT ATGGCAATA AGAGGCTCGA AAGTCCCGGT

```

Figure 5F: V heavy chain 5 (VH5) gene sequence (continued)

```

V T I S A D K S I S T A Y L Q W
BstEII
~~~~~
GGTGACCATT AGCGCGGATA AAAGCATTAG CACCGCGTAT CTTCAATGGA
CCACTGGTAA TCGCGCCTAT TTTCGTAATC GTGGCGCATA GAAGTTACCT

S   S   L   K   A   S   D   T   A   M   Y   Y   C   A   R   W   G
                               BssHII
                               ~~~~~
GCAGCCTGAA AGCGAGCGAT ACGGCCATGT ATTATTGCGC GCGTTGGGGC
CGTCGGACTT TCGCTCGCTA TGCCGGTACA TAATAACGCG CGCAACCCCG

G D G F Y A M D Y W G Q G T L V T
 StyI
                               ~~~~~
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

V   S   S
      BlnI
      ~~~~~
GGTTAGCTCA G
CCAATCGAGT C

```

Figure 5G: V heavy chain 6 (NH6) gene sequence

```

Q V Q L Q Q S G P G L V K P S Q T
MfeI
~~~~~
CAGGTGCAAT TGCAACAGTC TGGTCCGGGC CTGGTGAAC CGAGCCAAAC
GTCCACGTTA ACGTTGTCAG ACCAGGCCCG GACCACTTG GCTCGGTTTG

L S L T C A I S G D S V S S N S
BspEI
~~~~~
CCTGAGCCTG ACCTGTGCCA TTTCGGGAGA TAGCGTGAGC AGCAACAGCG
GGA CTGGAC TGGACACGCT AAAGGCCTCT ATCGCACTCG TCGTTGTCGC

A A W N W I R Q S P G R G L E W L
BstXI
~~~~~
XhoI
~~~~~
CGGCGTGGAA CTGGATTGCG CAGTCTCCTG GGCGTGGCCT CGAGTGGCTG
GCCGCACCTT GACCTAAGCG GTCAGAGGAC CCGCACCGGA GTCACCGAC

G R T Y Y R S K W Y N D Y A V S V
GGCCGTACCT ATTATCGTAG CAAATGGTAT AACGATTATG CCGTGAGCGT
CCGGCATGGA TAATAGCATC GTTACCATA TTGCTAATAC GCCACTCGCA

```

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Figure 5G: V heavy chain 6 (VH6) gene sequence (continued)

|                                                         |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
|---------------------------------------------------------|---|---|---|---|---|---|---|---|---|-------|--------|---|---|---|---|--|
| K                                                       | S | R | I | T | I | N | P | D | T | S     | K      | N | Q | F | S |  |
|                                                         |   |   |   |   |   |   |   |   |   | NspV  |        |   |   |   |   |  |
| BsaBI                                                   |   |   |   |   |   |   |   |   |   | ~~~~~ |        |   |   |   |   |  |
| GAAAAGCCCG ATTACCATCA ACCCGGATAC TTCGAAAAAC CAGTTTAGCC  |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| CTTTTCGGCC TAATGGTAGT TGGGCCTATG AAGCTTTTGTG GTCAAATCGG |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| L                                                       | Q | L | N | S | V | T | P | E | D | T     | A      | V | Y | C | A |  |
|                                                         |   |   |   |   |   |   |   |   |   | EagI  | BssHII |   |   |   |   |  |
| TGCAACTGAA CAGCGTGACC CCGGAAGATA CGGCCGTGTA TTATTGCGCG  |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| ACGTTGACTT GTCGCACTGG GGCCTTCTAT GCCGGCACAT AATAACGCGC  |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| R                                                       | W | G | G | D | G | F | Y | A | M | D     | Y      | W | G | Q | T |  |
| BssHII                                                  |   |   |   |   |   |   |   |   |   | StyI  |        |   |   |   |   |  |
| CGTTGGGCG GCGATGGCTT TTATGCGATG GATTATTGGG GCCAAGGCAC   |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| GCAACCCCGC CGCTACCGAA AATACGCTAC CTAATAACCC CGGTCCGTG   |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| L                                                       | V | T | V | S | S |   |   |   |   |       |        |   |   |   |   |  |
| BlpI                                                    |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| ~~~~~                                                   |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| CCTGGTGACG GTTAGCTCAG                                   |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |
| GGACCACTGC CAATCGAGTC                                   |   |   |   |   |   |   |   |   |   |       |        |   |   |   |   |  |

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Figure 6: oligonucleotides for gene synthesis

**O1K1** 5' - GAATGCATACGCTGATATCCAGATGACCCAGAG-  
CCCGTCTAGCCTGAGC -3'

**O1K2** 5' - CGCTCTGCAGGTAATGGTCACACGATCACCCAC-  
GCTCGCGCTCAGGCTAGACGGGC -3'

**O1K3** 5' - GACCATTACCTGCAGAGCGAGCCAGGGCATTAG-  
CAGCTATCTGGCGTGGTACCAGCAG -3'

**O1K4** 5' - CTTTGCAAGCTGCTGGCTGCATAAATTAATAGT-  
TTCGGTGCTTTACCTGGTTTCTGCTGGTACCACGCCAG -3'

**O1K5** 5' - CAGCCAGCAGCTTGCAAAGCGGGGTCCCGTCCC-  
GTTTTAGCGGCTCTGGATCCGGCACTGATTTTAC -3'

**O1K6** 5' - GATAATAGGTCGCAAAGTCTTCAGGTTGCAGGC-  
TGCTAATGGTCAGGGTAAAATCAGTGCCGGATCC -3'

**O2K1** 5' - CGATATCGTGATGACCCAGAGCCCACTGAGCCT-  
GCCAGTGACTCCGGGCGAGCC -3'

**O2K2** 5' - GCCGTTGCTATGCAGCAGGCTTTGGCTGCTTCT-  
GCAGCTAATGCTCGCAGGCTCGCCCGGAGTCAC -3'

**O2K3** 5' - CTGCTGCATAGCAACGGCTATAACTATCTGGAT-  
TGGTACCTTCAAAAACCAGGTCAAAGCCC -3'

**O2K4** 5' - CGATCCGGGACCCCACTGGCACGGTTGCTGCCC-  
AGATAAATTAATAGCTGCGGGCTTTGACCTGGTTTTTG -3'

**O2K5** 5' - AGTGGGGTCCCGGATCGTTTTAGCGGCTCTGGA-  
TCCGGCACCGATTTTACCCTGAAAATTAGCCGTGTG -3'

**O2K6** 5' - CCATGCAATAATACACGCCACGTCTTCAGCTT-  
CCACACGGCTAATTTTCAGGG -3'

**O3K1** 5' - GAATGCATACGCTGATATCGTGCTGACCCAGAG-  
CCCGG -3'

**O3K2** 5' - CGCTCTGCAGCTCAGGGTCGCACGTTGCCCCG-  
AGACAGGCTCAGGGTCGCCGGGCTCTGGGTCAGC -3'

**O3K3** 5' - CCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCA-  
GCAGCTATCTGGCGTGGTACCAG -3'

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Figure 6: (continued)

**O3K4** 5' - GCACGGCTGCTCGCGCCATAAATTAATAGACGC-  
GGTGCTTGACCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

**O3K5** 5' - GCGCGAGCAGCCGTGCAACTGGGGTCCCGGCGC-  
GTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC -3'

**O3K6** 5' - GATAATACACCGCAAAGTCTTCAGGTTCCAGGC-  
TGCTAATGGTCAGGGTAAAATCCGTGCCGGATC -3'

**O4K1** 5' - GAATGCATACGCTGATATCGTGATGACCCAGAG-  
CCCGGATAGCCTGGCG -3'

**O4K2** 5' - GCTTCTGCAGTTAATGGTTCGCACGTTTCGCCCAG-  
GCTCACCGCCAGGCTATCCGGGC -3'

**O4K3** 5' - CGACCATTAAGTGCAGAAGCAGCCAGAGCGTGC-  
TGTATAGCAGCAACAACAAAACACTATCTGGCGTGGTACCAG -  
3'

**O4K4** 5' - GATGCCCAATAAATTAATAGTTTTCGGCGGCTGA-  
CCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

**O4K5** 5' - AAACATTAATTTATTGGGCATCCACCCGTGAA-  
AGCGGGGTCCCGGATCGTTTTAGCGGCTCTGGATCCGGCAC -  
3'

**O4K6** 5' - GATAATACACCGCCACGTCTTCAGCTTGCAGGG-  
ACGAAATGGTCAGGGTAAAATCAGTGCCGGATCCAGAGCC -  
3'

**O1L1** 5' - GAATGCATACGCTCAGAGCGTGCTGACCCAGCC-  
GCCTTCAGTGAGTGG -3'

**O1L2** 5' - CAATGTTGCTGCTGCTGCCGCTACACGAGATGG-  
TCACACGCTGACCTGGTGCGCCACTCACTGAAGGCGGC -3'

**O1L3** 5' - GGCAGCAGCAGCAACATTGGCAGCAACTATGTG-  
AGCTGGTACCAGCAGTTGCCCGGGAC -3'

**O1L4** 5' - CCGGCACGCCTGAGGGACGCTGGTTGTTATCAT-  
AAATCAGCAGTTTCGGCGCCGTCCCGGGCAACTGC -3'

**O1L5** 5' - CCCTCAGGCGTGCCGGATCGTTTTAGCGGATCC-  
AAAAGCGGCACCAGCGCGAGCCTTGCG -3'

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Figure 6: (continued)

01L6 5' - CCGCTTCGTCTTCGCTTTGCAGGCCCGTAATCG-  
 CAAGGCTCGCGCTGG -3'  
 02L1 5' - GAATGCATACGCTCAGAGCGCACTGACCCAGCC-  
 AGCTTCAGTGAGCGGC -3'  
 02L2 5' - CGCTGCTAGTACCCGTACACGAGATGGTAATGC-  
 TCTGACCTGGTGAGCCGCTCACTGAAGCTGG -3'  
 02L3 5' - GTACGGGTACTAGCAGCGATGTGGGCGGCTATA-  
 ACTATGTGAGCTGGTACCAGCAGCATCCCGG -3'  
 02L4 5' - CGCCTGAGGGACGGTTGCTCACATCATAAATCA-  
 TCAGTTTCGGCGCCTTCCCGGGATGCTGCTGGTAC -3'  
 02L5 5' - CAACCGTCCCTCAGGCGTGAGCAACCGTTTGTAG-  
 CGGATCCAAAAGCGGCAACACCGCGAGCC -3'  
 02L6 5' - CCGCTTCGTCTTCCGCTTGCAGGCCGCTAATGG-  
 TCAGGCTCGCGGTGTTGCCG -3'  
 03L1 5' - GAATGCATACGCTAGCTATGAACTGACCCAGCC-  
 GCCTTCAGTGAGCG -3'  
 03L2 5' - CGCCCAGCGCATCGCCGCTACACGAGATACGCG-  
 CGGTCTGACCTGGTGCAACGCTCACTGAAGGCGGC -3'  
 03L3 5' - GGCGATGCGCTGGGCGATAAATACGCGAGCTGG-  
 TACCAGCAGAAACCCGGGCAGGCGC -3'  
 03L4 5' - GCGTTCCGGGATGCCTGAGGGACGGTCAGAATC-  
 ATCATAAATCACCAGAACTGGCGCCTGCCCCGGGTTC -3'  
 03L5 5' - CAGGCATCCCGGAACGCTTTAGCGGATCCAACA-  
 GCGGCAACACCGCGACCCTGACCATTAGCGG -3'  
 03L6 5' - CCGCTTCGTCTTCCGCTTGCAGGCCGCTAATGG-  
 TCAGGGTC -3'  
 01246H1 5' - GCTCTTCACCCCTGTTACCAAAGCCCAG-  
 GTGCAATTG -3'  
 01AH2 5' - GGCTTTGCAGCTCACTTTCACGCTGCTGCCCCGG-  
 TTTTTCCTTCCGCGCCAGACTGAACCAATTGCACCTGGGC-  
 TTTG -3'

Figure 6: (continued)

**O1AH3** 5' - GAAAGTGAGCTGCAAAGCCTCCGGAGGGCACTTT-  
TAGCAGCTATGCGATTAGCTGGGTGCGCCAAGCCCCTGGGCAG  
GGTC -3'

**O1AH4** 5' - GCCCTGAAACTTCTGCGCGTAGTTCGCCGTGCC-  
AAAAATCGGAATAATGCCGCCCATCCACTCGAGACCCTGCCC-  
AGGGGC -3'

**O1AH5** 5' - GCGCAGAAGTTTCAGGGCCGGGTGACCATTACC-  
GCGGATGAAAGCACCAGCACC GCGTATATGGAAGT GAGCAGCC  
TGCG -3'

**O1ABH6** 5' - GCGCGCAATAATACACGGCCGTATCTTCGCT-  
ACGCAGGCTGCTCAGTTCC -3'

**O1BH2** 5' - GGCTTTGCAGCTCACTTTCACGCTCGCGCCCGG-  
TTTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACCTGGGC-  
TTTG -3'

**O1BH3** 5' - GAAAGTGAGCTGCAAAGCCTCCGGATATACCTT-  
TACCAGCTATTATATGCACTGGGTCCGCCAAGCCCCTGGGCAG  
GGTC -3'

**O1BH4** 5' - GCCCTGAAACTTCTGCGCGTAGTTCGTGCCGCC-  
GCTATTCGGGTTAATCCAGCCCATCCACTCGAGACCCTGCCCCA  
GGGGC -3'

**O1BH5** 5' - GCGCAGAAGTTTCAGGGCCGGGTGACCATGACC-  
CGTGATACCAGCATTAGCACCGCGTATATGGAAGT GAGCAGCC  
TGCG -3'

**O2H2** 5' - GGTACAGGTCAGGGTCAGGGTTTGGGTCCGTTT-  
CACCAGGGCCGGGCGCTTTCTTTCAATTGCACCTGGGCTTTG  
-3'

**O2H3** 5' - CTGACCCTGACCTGTACCTTTTCCGGATTTAGC-  
CTGTCCACGTCTGGCGTTGGCGTGGGCTGGATTCGCCAGCCGC  
CTGGGAAAG -3'

**O2H4** 5' - GCGTTTTTCAGGCTGGTGCTATAATACTTATCAT-  
CATCCCAATCAATCAGAGCCAGCCACTCGAGGGCTTTCCCAGG  
CGGCTGG -3'

Figure 6: (continued)

**O2H5** 5' - GCACCAGCCTGAAAACGCGTCTGACCATTAGCA-  
AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACAT  
GG -3'

**O2H6** 5' - GCGCGCAATAATAGGTGGCCGTATCCACCGGGT-  
CCATGTTGGTCATAGTCAGC -3'

**O3H1** 5' - CGAAGTGCAATTGGTGGAAAGCGGCGGCGGCCT-  
GGTGCAACCGGGCGGCAG -3'

**O3H2** 5' - CATAGCTGCTAAAGGTAAATCCGGAGGCCGCGC-  
AGCTCAGACGCAGGCTGCCGCCCGGTTGCAC -3'

**O3H3** 5' - GATTTACCTTTAGCAGCTATGCGATGAGCTGGG-  
TGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAG -3'

**O3H4** 5' - GGCCTTTCACGCTATCCGCATAATAGGTGCTGC-  
CGCCGCTACCGCTAATCGCGCTCACCCACTCGAGACCC -3'

**O3H5** 5' - CGGATAGCGTGAAAGGCCGTTTTACCATTTTCAC-  
GTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAG-3'

**O3H6** 5' - CACGCGCGCAATAATACACGGCCGTATCTTCCG-  
CACGCAGGCTGTTTCATTTGCAGATACAGG -3'

**O4H2** 5' - GGTCAGGCTCAGGGTTTCGCTCGGTTTCACCAG-  
GCCCCGACCACTTTCTTGCAATTGCACCTGGGCTTTG -3'

**O4H3** 5' - GAAACCCTGAGCCTGACCTGCACCGTTTCCGGA-  
GGCAGCATTAGCAGCTATTATTGGAGCTGGATTGCCAGCCGC  
-3'

**O4H4** 5' - GATTATAGTTGGTGCTGCCGCTATAATAAATAT-  
AGCCAATCCACTCGAGACCCTTCCCAGGCGGCTGGCGAATCCA  
G -3'

**O4H5** 5' - CGGCAGCACCAACTATAATCCGAGCCTGAAAAG-  
CCGGGTGACCATTAGCGTTGATACTTCGAAAAACCAGTTTAGC  
CTG -3'

**O4H6** 5' - GCGCGCAATAATACACGGCCGTATCCGCCGCCG-  
TCACGCTGCTCAGTTTCAGGCTAAACTGGTTTTTCG -3'

Figure 6: (continued)

**O5H1** 5' - GCTCTTCACCCCTGTTACCAAAGCCGAAGTGCA-  
ATTG -3'

**O5H2** 5' - CCTTTGCAGCTAATTTTCAGGCTTTCGCCCCGGT-  
TTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACTTCGGCTT  
TGG -3'

**O5H3** 5' - CCTGAAAATTAGCTGCAAAGGTTCCGGATATTC-  
CTTTACGAGCTATTGGATTGGCTGGGTGCGCCAGATGCCTGG  
-3'

**O5H4** 5' - CGGAGAATAACGGGTATCGCTATCGCCCCGGATA-  
AATAATGCCCATCCACTCGAGACCCTTCCCAGGCATCTGGCGC  
AC -3'

**O5H5** 5' - CGATACCCGTTATTCTCCGAGCTTTCAGGGCCA-  
GGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTT  
C -3'

**O5H6** 5' - GCGCGCAATAATACATGGCCGTATCGCTCGCTT-  
TCAGGCTGCTCCATTGAAGATACGCGGTGCTAATG -3'

**O6H2** 5' - GAAATCGCACAGGTCAGGCTCAGGGTTTGGCTC-  
GGTTTCACCAGGCCCGGACCAGACTGTTGCAATTGCACCTGG-  
GCTTTG -3'

**O6H3** 5' - GCCTGACCTGTGCGATTTCCGGAGATAGCGTGA-  
GCAGCAACAGCGCGGCGTGGAAGTGGATTCCGCCAGTCTCCTGG  
GCG -3'

**O6H4** 5' - CACCGCATAATCGTTATAACCATTTGCTACGATA-  
ATAGGTACGGCCCAGCCACTCGAGGCCACGCCCAGGAGACTG-  
GCG -3'

**O6H5** 5' - GGTATAACGATTATGCGGTGAGCGTGAAAAGCC-  
GGATTACCATCAACCCGGATACTTCGAAAAACCAGTTTAGCCT  
GC -3'

**O6H6** 5' - GCGCGCAATAATACACGGCCGTATCTTCCGGGG-  
TCACGCTGTTCAAGTTGCAGGCTAAACTGGTTTTTC -3'

**OCLK1** 5' - GGCTGAAGACGTGGGCGTGTATTATTGCCAGCA-  
GCATTATACCACCCCGCCGACCTTTGGCCAGGGTAC -3'

Figure 6: (continued)

**OCLK2** 5' - GCGGAAAAATAAACACGCTCGGAGCAGCCACCG-  
TACGTTTAATTTCAACTTTTCGTACCCTGGCCAAAGGTC -3'

**OCLK3** 5' - GAGCGTGTTTATTTTTCCGCCGAGCGATGAACA-  
ACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTG -3'

**OCLK4** 5' - CAGCGCGTTGTCTACTTTCCACTGAACTTTTCGC-  
TTCACGCGGATAAAAGTTGTTTCAGCAGGCACACCACGC -3'

**OCLK5** 5' - GAAAGTAGACAACGCGCTGCAAAGCGGCAACAG-  
CCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAG -3'

**OCLK6** 5' - GTTTTTCATAATCCGCTTTGCTCAGGGTCAGGG-  
TGCTGCTCAGAGAATAGGTGCTATCTTTGCTATCCTGTTCG -  
3'

**OCLK7** 5' - GCAAAGCGGATTATGAAAAACATAAAGTGTATG-  
CGTGCGAAGTGACCCATCAAGGTCTGAGCAGCCCGGTG -3'

**OCLK8** 5' - GGCATGCTTATCAGGCCTCGCCACGATTAAAAG-  
ATTTAGTCACCGGGCTGCTCAGAC -3'

**OCH1** 5' - GGCGTCTAGAGGCCAAGGCACCCTGGTGACGGT-  
TAGCTCAGCGTCGAC -3'

**OCH2** 5' - GTGCTTTTGCTGCTCGGAGCCAGCGGAAACACG-  
CTTGGACCTTTGGTCGACGCTGAGCTAACC -3'

**OCH3** 5' - CTCCGAGCAGCAAAAGCACCCAGCGGCGGCACGG-  
CTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC -3'

**OCH4** 5' - CTGGTCAGCGCCCCGCTGTTCCAGCTCACGGTG-  
ACTGGTTCCGGGAAATAATCTTTAACCAGGCA -3'

**OCH5** 5' - AGCGGGGCGCTGACCAGCGGCGTGATACCTTT-  
CCGGCGGTGCTGCAAAGCAGCGGCCTG -3'

**OCH6** 5' - GTGCCTAAGCTGCTGCTCGGCACGGTCACAACG-  
CTGCTCAGGCTATACAGGCCGCTGCTTTGCAG -3'

**OCH7** 5' - GAGCAGCAGCTTAGGCACTCAGACCTATATTTG-  
CAACGTGAACCATAAACCGAGCAACACC -3'

**OCH8** 5' - GCGCGAATTCGCTTTTCGGTTCCACTTTTTTAT-  
CCACTTTGGTGTGCTCGGTTTATGG -3'

Figure 7A: sequence of the synthetic Ck gene segment

```

° V A A A P S V F I F P P S D E Q
BsiWI
~~~~~
CGTACGGTGG CTGCTCCGAG CGTGTATTATT TTCCGCCGA GCGATGAACA
GCATGCCACC GACGAGGCTC GCACAAATAA AAAGCGGCT CGCTACTTGT

L K S G T A S V V C L L N N F Y
ACTGAAAAGC GGCACGGCGA GCGTGGTGTG CCTGCTGAAC AACTTTTATC
TGACTTTTCG CCGTGCCGCT CGCACACACAC GGACGACTTG TTGAAAATAG

P R E A K V Q W K V D N A L Q S G
CGCGTGAAGC GAAAGTTCAG TGGAAAGTAG ACAACGCGCT GCAAAGCGGC
GCGCACTTCG CTTCAAGTC ACCTTTCATC TGTGCGCGA CGTTTCGCCG

N S Q E S V T E Q D S K D S T Y S
AACAGCCAGG AAAGCGTGAC CGAACAGGAT AGCAAAGATA GCACCTATTC
TTGTCGGTCC TTTCGCACTG GCTTGTCCCTA TCGTTTCTAT CGTGGATAAG

L S S T L T L S K A D Y E K H K
TCTGAGCAGC ACCCTGACCC TGAGCAAAGC GGATTATGAA AAACATAAAG
AGACTCGTCG TGGGACTGGG ACTCGTTTCG CCTAATACTT TTTGTATTTC

```

Figure 7A: sequence of the synthetic Cx gene segment (continued)

V Y A C E V T H Q G L S S P V T K  
 TGTATGCGTG CGAAGTGACC CATCAAGGTC TGAGCAGCCCC GTGACTAAA  
 ACATACGCAC GCTTCACTGG GTAGTCCAG ACTCGTCGGG CCACTGATTT

S F N R G E A \*  
 StuI SphI  
 -----  
 TCCTTTAATC GTGGCGAGGC CTGATAAGCA TGC  
 AGAAAAATTAG CACCGCTCCG GACTATTTCGT ACG



Figure 78: sequence of the synthetic CH1 gene segment

```

      A  S  T  K  G  P  S  V  F  P  L  A  P  S  S
BlpI  Sali
~~~~~
GTCAGCGTC GACCAAGGT CCAAGCGTGT TTCCGCTGGC TCCGAGCAGC
CGAGTCGCAG CTGGTTCCA GGTTCGCACA AAGCGACCG AGGCTCGTCG

 K S T S G G T A A L G C L V K D Y
AAAAGCACCA GCGCGGCAC GGCTGCCCTG GGCTGCCCTG TTAAGATTA
TTTTCGTGGT CGCCGCCGTG CCGACGGGAC CCGACGGACC AATTCTAAT

 F P E P V T V S W N S G A L T S
TTTCCCGGAA CCAGTCACCG TGAGCTGGAA CAGCGGGCG CTGACCAGCG
AAAGGCCCTT GTCAGTGGC ACTCGACCTT GTCGCCCCGC GACTGGTCGC

 G V H T F P A V L Q S S G L Y S L
GCGTGCATAC CTTCCGGCG GTGCTGCAA GCAGCGGCCT GTATAGCCTG
CGCACGTATG GAAAGGCCGC CACGACGTTT CGTCGCCGGA CATATCGGAC

 S S V V T V P S S S L G T Q T Y I
AGCAGCGTTG TGACCGTGCC GAGCAGCAGC TTAGGCACTC AGACCTATAT
TCGTCGCAAC ACTGGCACGG CTCGTCGTCG AATCCGTGAG TCTGGATATA

```

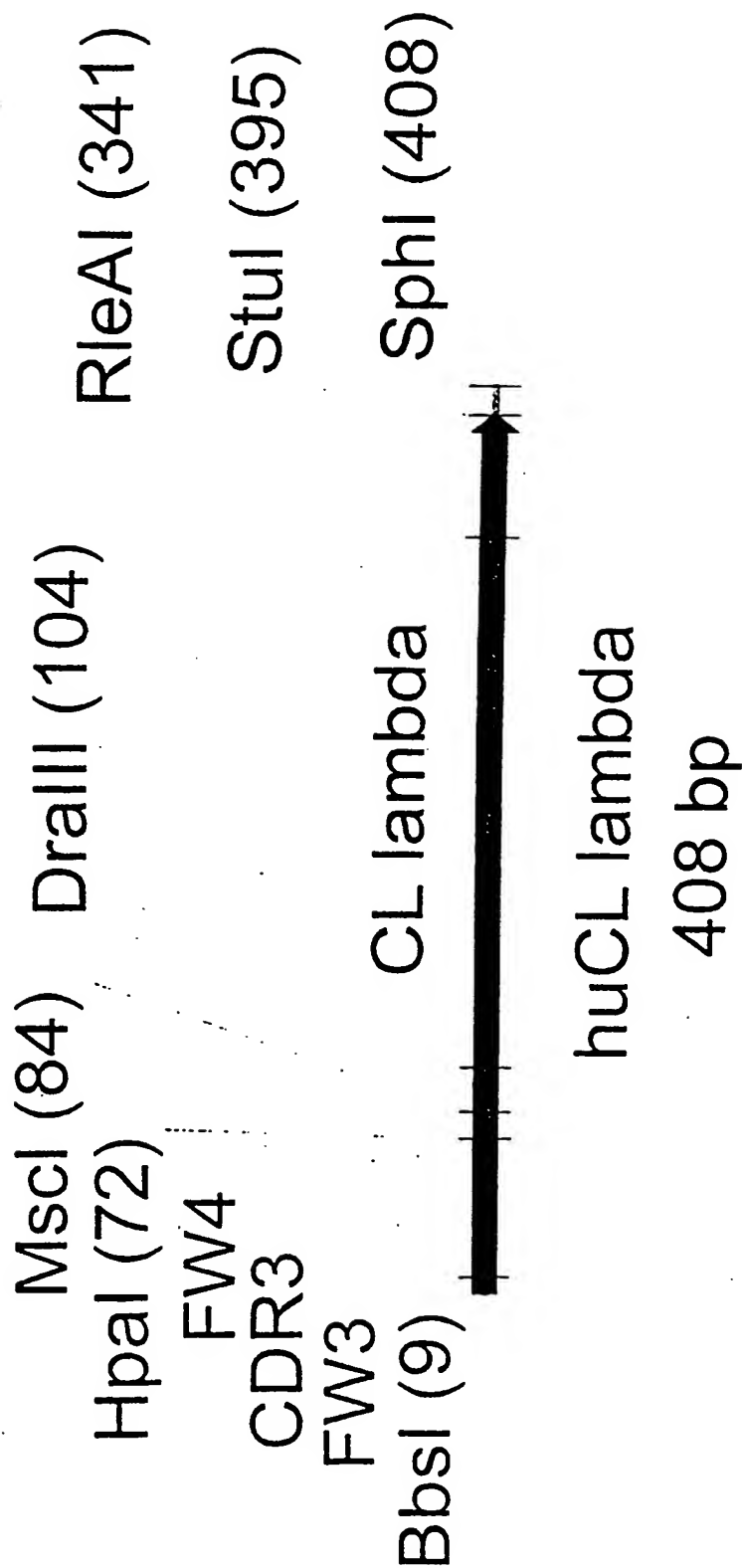
Figure 7B: sequence of the synthetic CH1 gene segment (continued)

|            |            |            |            |            |           |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|------------|------------|-----------|---|---|---|---|---|---|---|---|---|---|
| C          | N          | V          | N          | H          | K         | P | S | N | T | K | V | D | K | K | V |
| TTGCAACGTG | AACCATAAAC | CGAGCAACAC | CAAAGTGGAT | AAAAAAGTGG | TTTTCACCC |   |   |   |   |   |   |   |   |   |   |
| AACGTTGCAC | TTGGTATTG  | GCTCGTTGTG |            |            |           |   |   |   |   |   |   |   |   |   |   |

|            |            |         |   |       |   |         |
|------------|------------|---------|---|-------|---|---------|
| E          | P          | K       | S | E     | F | *       |
|            |            |         |   | ECORI |   | HindIII |
|            |            |         |   | ~~~~~ |   | ~~~~~   |
| AACCGAAAAG | CGAATTCTGA | TAAGCTT |   |       |   |         |
| TTGGCTTTC  | GCTTAAGACT | ATTCGAA |   |       |   |         |

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Figure 7C: functional map and sequence of module 24 comprising the synthetic Cλ gene segment (huCL lambda)



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Figure 7C: functional map and sequence of module 24 comprising the synthetic Cl gene segment (huCl lambda) (continued)

| Bbs I   |                                                                                                                    | Hpa I |  | Msc I |  | Dra III |  |
|---------|--------------------------------------------------------------------------------------------------------------------|-------|--|-------|--|---------|--|
| ~~~~~   |                                                                                                                    | ~~~~~ |  | ~~~~~ |  | ~~~~~   |  |
| 1       | GAAGACGAAG CGGATTATTA TTGCCAGCAG CATTATACCA CCCCGCCTGT<br>CTTCTGCTTC GCCTAATAAT AACGGTCGTC GTAATATGGT GGGCGGGACA   |       |  |       |  |         |  |
| 51      | GTTTGGCGGC GGCACGAAGT TAACCGTTCT TGGCCAGCCG AAAGCCGCAC<br>CAAACCGCCG CCGTGCTTCA ATTGGCAAGA ACCGGTCGGC TTTCGGCGTG   |       |  |       |  |         |  |
| Dra III |                                                                                                                    |       |  |       |  |         |  |
| ~~~~~   |                                                                                                                    |       |  |       |  |         |  |
| 101     | CGAGTGTGAC GCTGTTTCCG CCGAGCAGCG AAGAATTGCA GGCGAACAAA<br>GCTCACACTG CGACAAAGGC GGCTCGTCGC TTCTTAACGT CCGCTTGTTT   |       |  |       |  |         |  |
| 151     | GGGACCCCTGG TGTGCCCTGAT TAGCGACTTT TATCCGGGAG CCGTGACAGT<br>CGCTGGGACC ACACGGACTA ATCGCTGAAA ATAGGCCCTC GGCACTGTCA |       |  |       |  |         |  |
| 201     | GGCCTGGAAG GCAGATAGCA GCCCCGTCAA GGCGGGAGTG GAGACCACCA<br>CCGGACCTTC CGTCTATCGT CGGGGCAGTT CCGCCCTCAC CTCTGGTGGT   |       |  |       |  |         |  |

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Figure 7C: functional map and sequence of module 24 comprising the synthetic CI gene segment (huCL lambda) (continued)

251 CACCCTCCAA ACAAGCAAC AACAGTACG CGGCCAGCAG CTATCTGAGC  
GTGGAGGTT TGTTTCGTTG TTGTTCAATGC GCCGGTCGTC GATAGACTCG

RleAI

~~~~~

301 CTGACGCCCTG AGCAGTGGAA GTCCACACAGA AGTACAGCT GCCAGGTCAC  
GACTGCGGAC TCGTCACCTT CAGGGTGTCT TCGATGTCTGA CGGTCCAGTG

StuI

~~~~~

351 GCATGAGGGG AGCACCGTGG AAAAAACCGT TGCGCCGACT GAGGCCTGAT  
CGTACTCCCC TCGTGGCACC TTTT TTGGCA ACGCGGCTGA CTCCGGACTA

SphI

~~~~~

401 AAGCATGC  
TTCGTACG

Figure 7D: oligonucleotides used for synthesis of module M24 containing Cλ gene segment

M24: assembly PCR

M24-A: GAAGACAAGCGGATTATTGCCAGCAGCATTATACACCCGCCCTGTGTTGGCGGCG-

GCACGAAGTTAACCGTTC

M24-B: CAATTCTTCGCTGCTCGGCGGAACAGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAA-

GAACGGTAACTTCGTGCCGC

M24-C: CGCCGAGCAGCGAAGAAATTCAGGCGAACAAGGACCCCTGGGTGCTGATTAGCGACT-

TTATCCGGGAGCCGTGACA

M24-D: TGTGAGGGGTGGTGGTCTCCACTCCCGCTTGACGGGGCTGCTATCTGCTTCCAG-

GCCACTGTCACGGCTCCCGG

M24-E: CCACACCCCTCCAAACAAGCAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC-

CTGAGCAGTGAAGTCCCACAGAAGCTACAGCTG

M24-F: GCATGCTTATCAGGCCTCAGTCGGCGCAACGGTTTTTCCACGGTGTCTCCCCCTCATGCGT-

GACCTGGCAGCTGTAGCTTC

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2

|                                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|----------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M                                                        | K | Q | S | T | I | A | L | A | L | L | P | L | L | F | T | P |
|                                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SapI                                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| -----                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ATGAAACAAA GCACTATTGC ACTGGCACTC TTACCGTTGC TCTTCACCCC   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TACTTTGTTT CGTGATAACG TGACCGTGAG AATGGCAACG AGAAGTGGGG   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| V                                                        | T | K | A | D | Y | K | D | E | V | Q | L | V | E | S | G |   |
| MfeI                                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| -----                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TGTTACCAA GCCGACTACA AAGATGAAGT GCAATTGGTG GAAAGCGGCG    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ACAATGGTTT CGGCTGATGT TTCTACTTCA CGTTAACAC CTTTCGCCGC    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| G                                                        | G | L | V | Q | P | G | G | S | L | R | L | S | C | A | A | S |
| BspEI                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| -----                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| GCGGCCCTGGT GCAACCGGGC GGCAGCCTGC GTCTGAGCTG CGCGGCCCTCC |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CGCCGGACCA CGTTGGCCCG CCGTCGGACG CAGACTCGAC GCGCCGGAGG   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| G                                                        | F | T | F | S | S | Y | A | M | S | W | V | R | Q | A | P | G |
| BspEI                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| -----                                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| GGATTACCT TTAGCAGCTA TCGGATGAGC TGGGTGCGCC AAGCCCCTGG    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CCTAAATGGA AATCGTCGAT ACGTACTCG ACCACGCGG TTCGGGGACC     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

|                                                         |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
|---------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|-------|---|---|---|
| K                                                       | G | L | E | W | V | S | A | I | S | G | S     | G | S | T |
| XhoI                                                    |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| ~~~~~                                                   |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| GAAGGGTCTC GAGTGGGTGA GCGCGATTAG CCGTAGCGGC GGCAGCACCT  |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| CTCCACAGAG CTCACCCACT CCGGCTAATC GCCATCGCCG CCGTCGTGGA  |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| Y                                                       | Y | A | D | S | V | K | G | R | F | T | I     | S | R | D |
|                                                         |   |   |   |   |   |   |   |   |   |   | NspV  |   |   |   |
|                                                         |   |   |   |   |   |   |   |   |   |   | PmlI  |   |   |   |
|                                                         |   |   |   |   |   |   |   |   |   |   | ~~~~~ |   |   |   |
| ATTATGCCGA TAGCGTGAAA GGCCGTTTTC CCATTTCACG TGATAATTTCG |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| TAATACGCCCT ATCGCACTTT CCGGC AAAAT GTAAAGTGC ACTATTAAGC |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| K                                                       | N | T | L | Y | L | Q | M | N | S | L | R     | A | E | D |
| NspV                                                    |   |   |   |   |   |   |   |   |   |   |       | T | A |   |
| ~~~                                                     |   |   |   |   |   |   |   |   |   |   | EagI  |   |   |   |
| ~~~~~                                                   |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| AAAAACACCC TGTATCTGCA AATGAACAGC CTGCGTGCGG AAGATACGGC  |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| TTTTTGTGGG ACATAGACGT TTA CTGTGCG GACGCACGCC TTCTATGCCG |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| V                                                       | Y | Y | C | A | R | W | G | G | D | G | F     | Y | A | M |
| EagI                                                    |   |   |   |   |   |   |   |   |   |   |       | D |   |   |
| BssHII                                                  |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| ~~~~~                                                   |   |   |   |   |   |   |   |   |   |   |       |   |   |   |
| CGGTATTAT TCGCGCGCGTT GGGCGGCGCA TGGCTTTTAT GCGATGGATT  |   |   |   |   |   |   |   |   |   |   |       |   |   |   |

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

```

GCACATAATA ACGCGGCAA CCGCGCGCT ACCGAAAATA CGTACCTAA
Y W G Q G T L V T V S S A G G G S
 BlnI

ATTGGGGCCA AGCACCCCTG GTGACGGTTA GCTCAGCGGG TGGCGGTTCT
TAACCCCGGT TCCGTGGGAC CACTGCCAAT CGAGTCGCCC ACCGCCAAGA

G G G G S G G G G S G G G S D I
EcoRV

GGCGGCGGTG GGAGCGGTGG CCGTGGTTCT GGCGGTGGTG GTTCCGATAT
CCGCCGCCAC CCTCGCCACC GCCACCAAGA CCGCCACCAC CAAGGCTATA

V M T Q S P L S L P V T P G E P
EcoRV

CGTGATGACC CAGAGCCCCAC TGAGCCTGCC AGTGACTCCG GGCGAGCCTG
GCACTACTGG GTCTCGGGTG ACTCGGACGG TCACTGAGGC CCGCTCGGAC

A S I S C R S S Q S L L H S N G Y
PstI

CGAGCATTAG CTGCAGAAGC AGCCAAAGCC TGCTGCATAG CAACGGCTAT
GCTCGTAATC GACGTCTTCG TCGGTTTCGG ACGACGTATC GTTGCCCGATA

```

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

```

N Y L D W Y L Q K P G Q S P Q L L AseI
 KpnI SexAI

AACTATCTGG ATTGGTACCT TCAAAAACCA GTCAAAGCC CGCAGCTATT
TTGATAGACC TAACCATGGA AGTTTTCGGT CCAGTTTCGG GCGTCGATAA

I Y L G S N R A S G V P D R F S
AseI

AATTATCTG GGCAGCAACC GTGCCAGTGG GTCCCAGGAT CGTTTAGCG
TTAAATAGAC CCGTCGTTGG CACGGTCACC CCAGGGCCTA GCAAATCGC

G S G S G T D F T L K I S R V E A
 BamHI

GCTCTGGATC CGGCACCGAT TTTACCCTGA AAATTAGCCG TGTGGAAGCT
CGAGACCTAG GCCGTGGCTA AAATGGGACT TTTAATCGGC ACACCTTCGA

E D V G V Y Y C Q Q H Y T P P T
BbsI

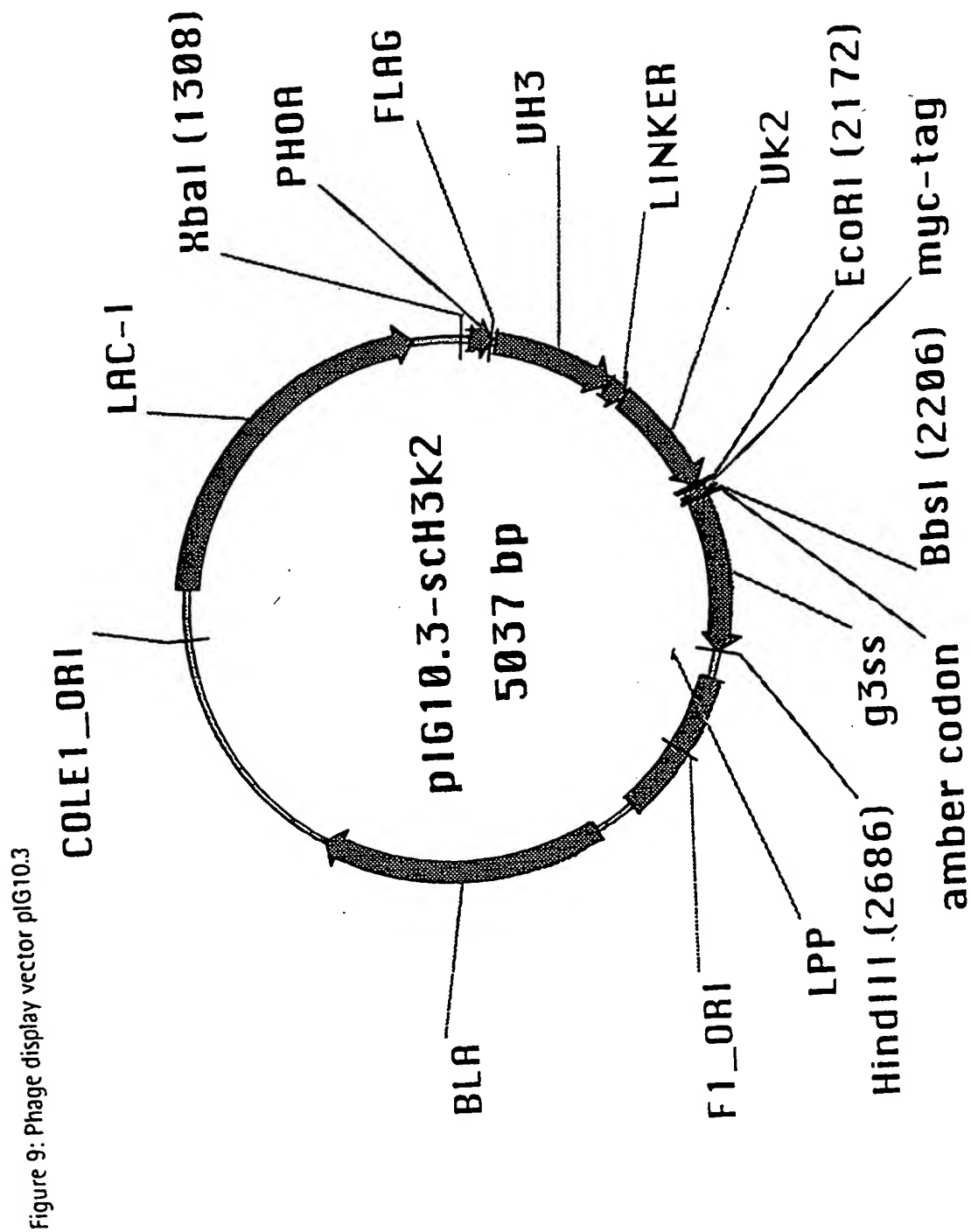
GAAGACGTGG GCGTGTATTA TTGCCAGCAG CATTATACCA CCCC GCCGAC
CTTCTGCACC CGCACATAAT AACGGTCGTC GTAATATGGT GGGCGGGCTG

```

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

|             |            |            |             |     |   |   |   |   |   |   |   |   |   |
|-------------|------------|------------|-------------|-----|---|---|---|---|---|---|---|---|---|
| F           | G          | Q          | G           | T   | K | V | E | I | K | R | T | E | F |
| MSCI        |            |            |             |     |   |   |   |   |   |   |   |   |   |
| -----       |            |            |             |     |   |   |   |   |   |   |   |   |   |
| CTTTGGCCAG  | GGTACGAAAG | TTGAAATTAA | ACGTACGGAA  | TTC |   |   |   |   |   |   |   |   |   |
| GAAACCGGTC  | CCATGCTTTC | AACTTTAATT | TGCATGCCCTT | AAG |   |   |   |   |   |   |   |   |   |
| BsiWI ECORI |            |            |             |     |   |   |   |   |   |   |   |   |   |
| -----       |            |            |             |     |   |   |   |   |   |   |   |   |   |



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Figure 10: Sequence analysis of initial libraries

|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|---|------|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 103  | W | W | W | W | W | W | W | W | W | W | W | W |
|   | 102  | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
|   | 101  | D | D | D | D | D | D | D | D | D | D | D | D |
|   | 100E | M | - | - | - | - | - | - | - | - | - | - | - |
|   | 100D | - | - | - | - | - | - | - | - | - | - | - | - |
|   | 100C | - | - | - | - | - | - | - | - | - | - | - | - |
|   | 100B | A | - | - | - | - | - | - | - | - | - | - | - |
|   | 100A | Y | - | - | - | - | - | - | - | - | - | - | - |
|   | 100  | F | Y | H | H | R | Y | P | - | S | K | A | D |
|   | 99   | G | N | W | Y | A | G | Q | R | N | S | A | Y |
|   | 98   | D | M | E | L | K | T | A | T | R | D | F | Q |
|   | 97   | G | K | T | E | L | T | E | I | N | G | T | P |
|   | 96   | G | G | R | R | F | N | N | A | Y | V | K | A |
|   | 95   | W | F | H | V | K | W | I | T | W | S | S | V |
|   | 94   | R | R | R | R | R | R | R | R | R | R | R | R |
| B | 93   | A | A | A | A | A | A | A | A | A | A | A | A |
|   | 92   | C | C | C | C | C | C | C | C | C | C | C | C |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|   |      |   |   |   |   |   |   |   |   |   |   |   |   |

Figure 10: Sequence analysis of initial libraries

|   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C | C | C | C | C | C | C | C | C | C | C | C | C |
| A | A | A | A | A | A | A | A | A | A | A | A | A |
| R | R | R | R | R | R | R | R | R | R | R | R | R |
| Y | M | K | T | Y | * | R | M | K | S | Y |   |   |
| F | A | N | Q | P | G | N | K | G | W | A |   |   |
| V | L | Q | S | Y | S | P | P | S | T | G |   |   |
| H | R | M | F | R | G | W | M | E | N | T |   |   |
| F | A | V | W | S | S | N | L | F | D | T |   |   |
| L | S | F | E | N | E | V | N | L | K | F |   |   |
| Y | G | H | Q | F | H | N | R | E | P | K |   |   |
| T | K | A | Q | F | W | Y | D | T | N | Q |   |   |
| M | Y | R | K | M | S | L | G | D | F | G |   |   |
| V | I | K | V | P | I | H | T | V | I | P |   |   |
| M | M | F | M | M | F | F | M | M | M | M |   |   |
| D | D | D | D | D | D | D | D | D | D | D |   |   |
| V | V | V | Y | V | V | V | V | Y | V | Y |   |   |
| W | W | W | W | W | W | W | W | W | W | W |   |   |

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Figure 11: Expression analysis of initial library

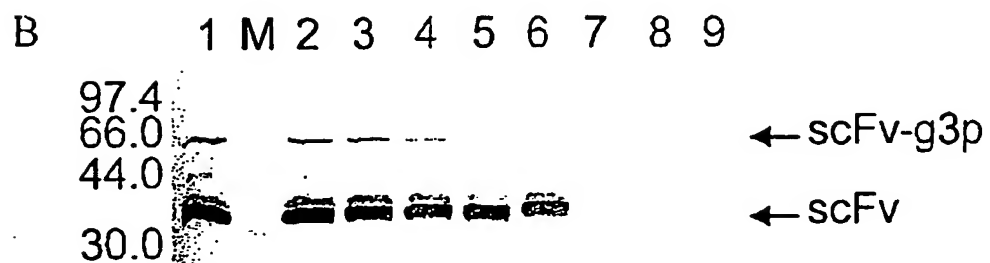
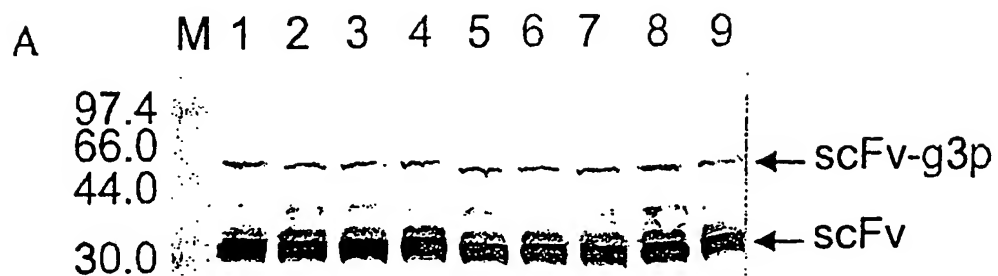


Figure 12: Increase of specificity during the panning rounds

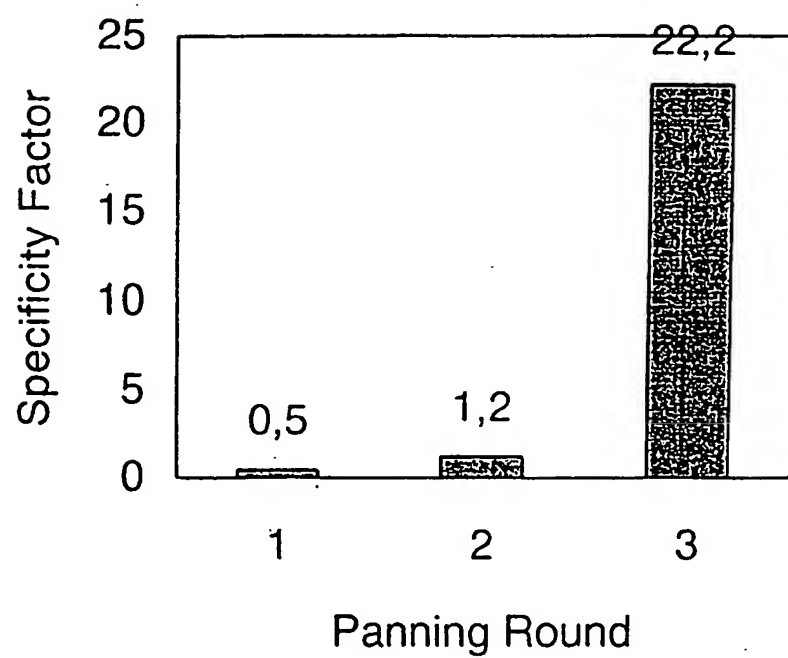




Figure 13: Phage ELISA of clones after the 3rd round of panning

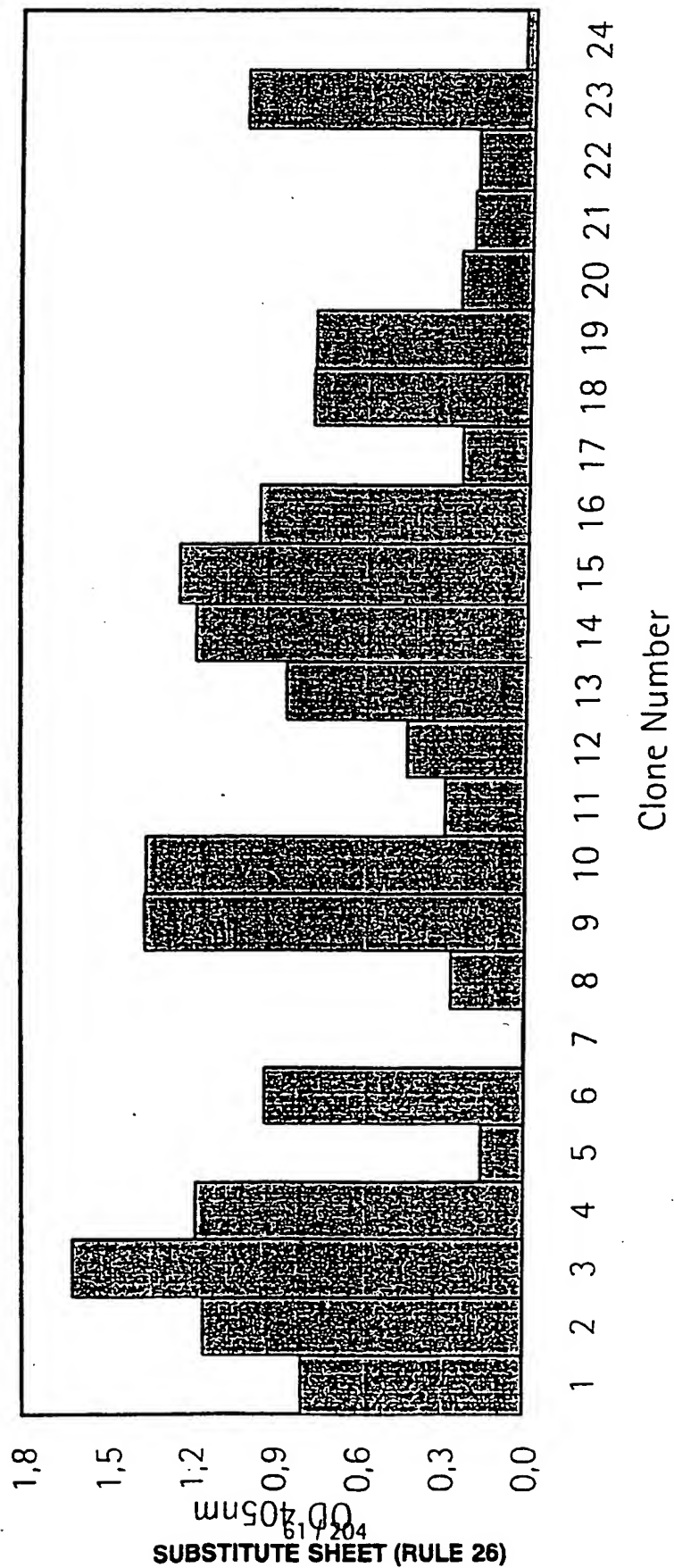
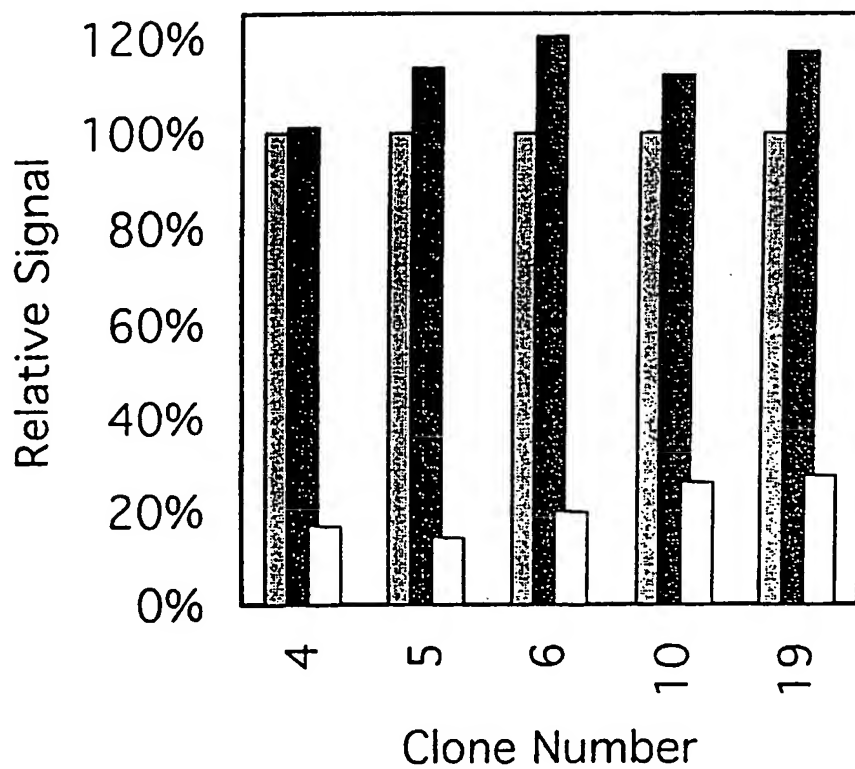


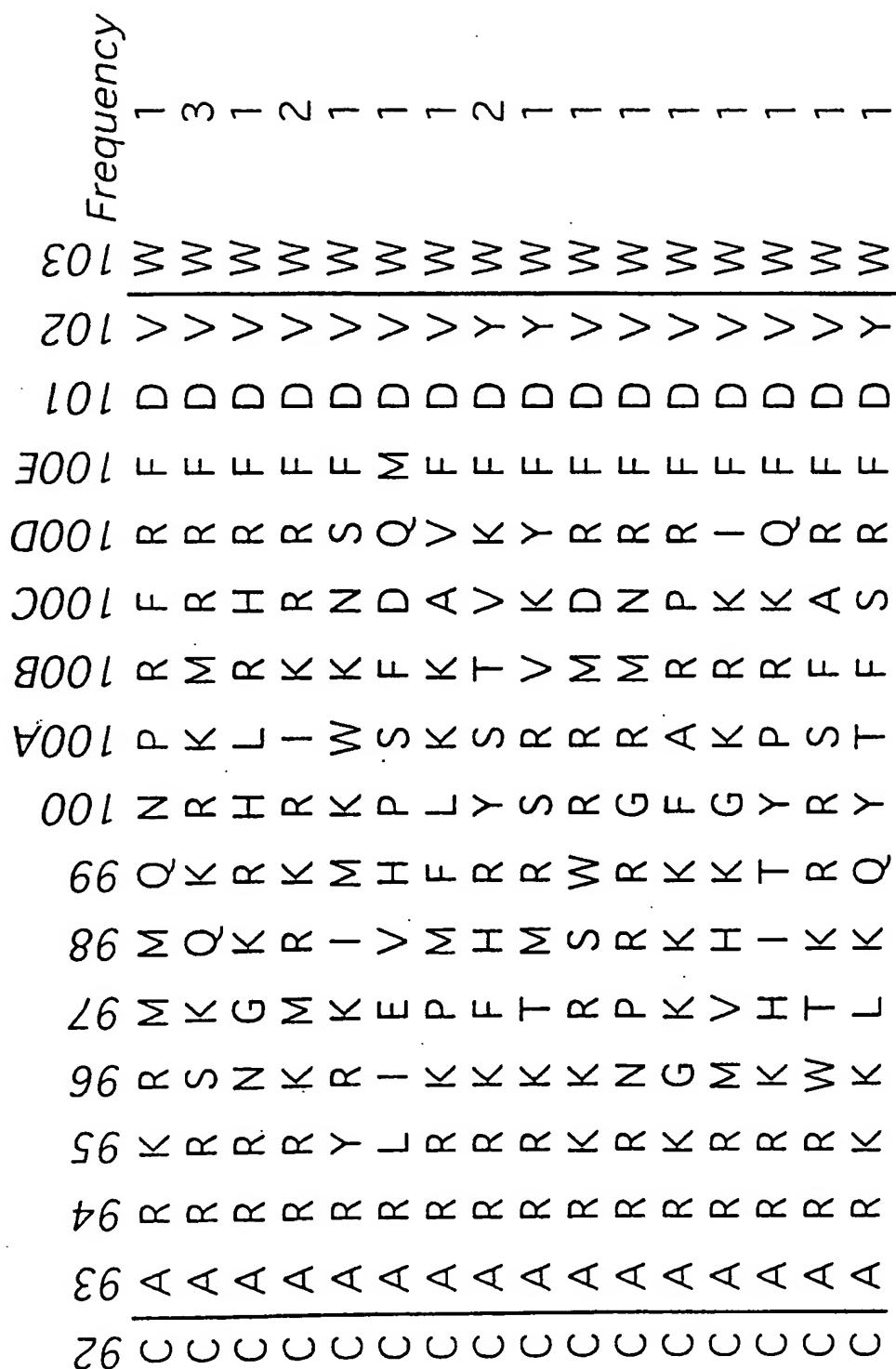
Figure 14: Competition ELISA



▨ No Inhibition

■ Inhibition with  
BSA

□ Inhibition with  
Fluorescein



**Figure 15: Sequence analysis of fluorescein binders**

Figure 16: Purification of fluorescein binding scFv fragments

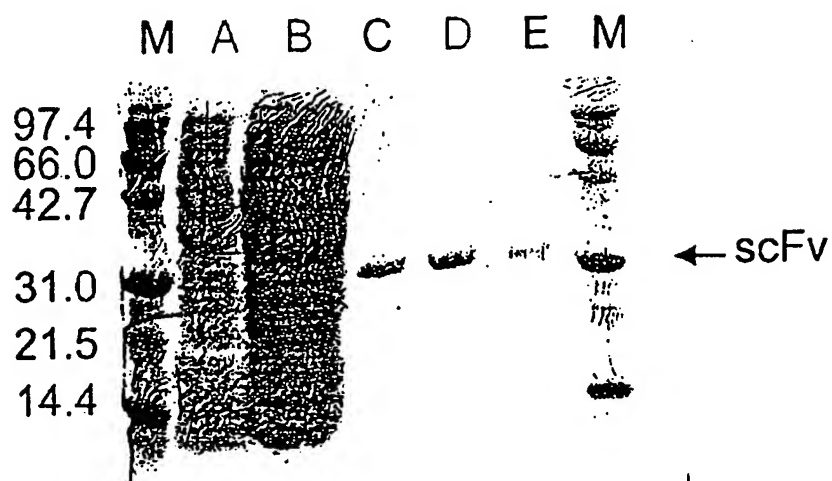
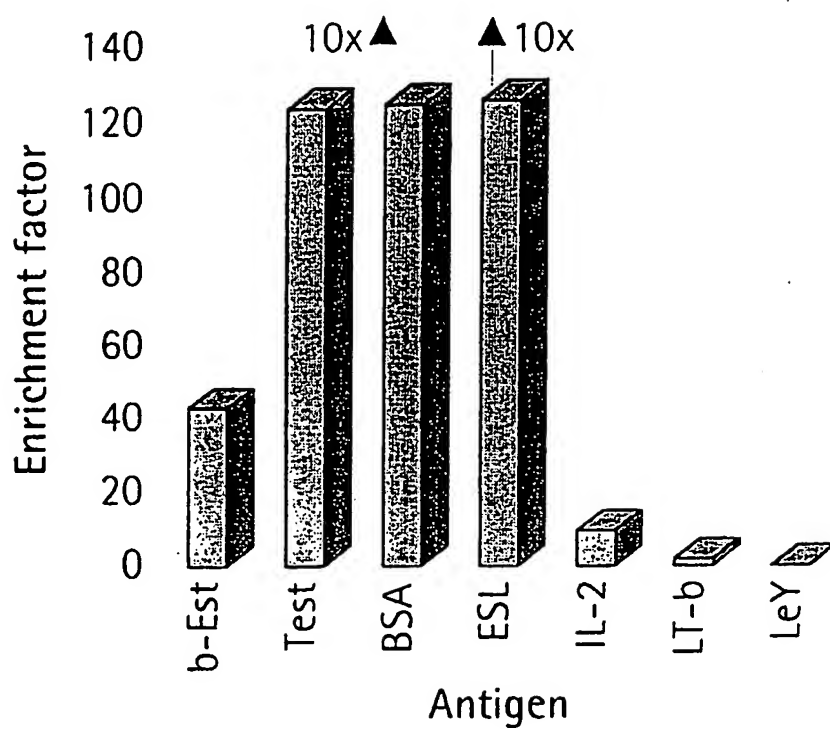


Figure 17: Enrichment factors after three rounds of panning



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anti- $\beta$ -estradiol antibodies

anti-ESL-1 antibodies

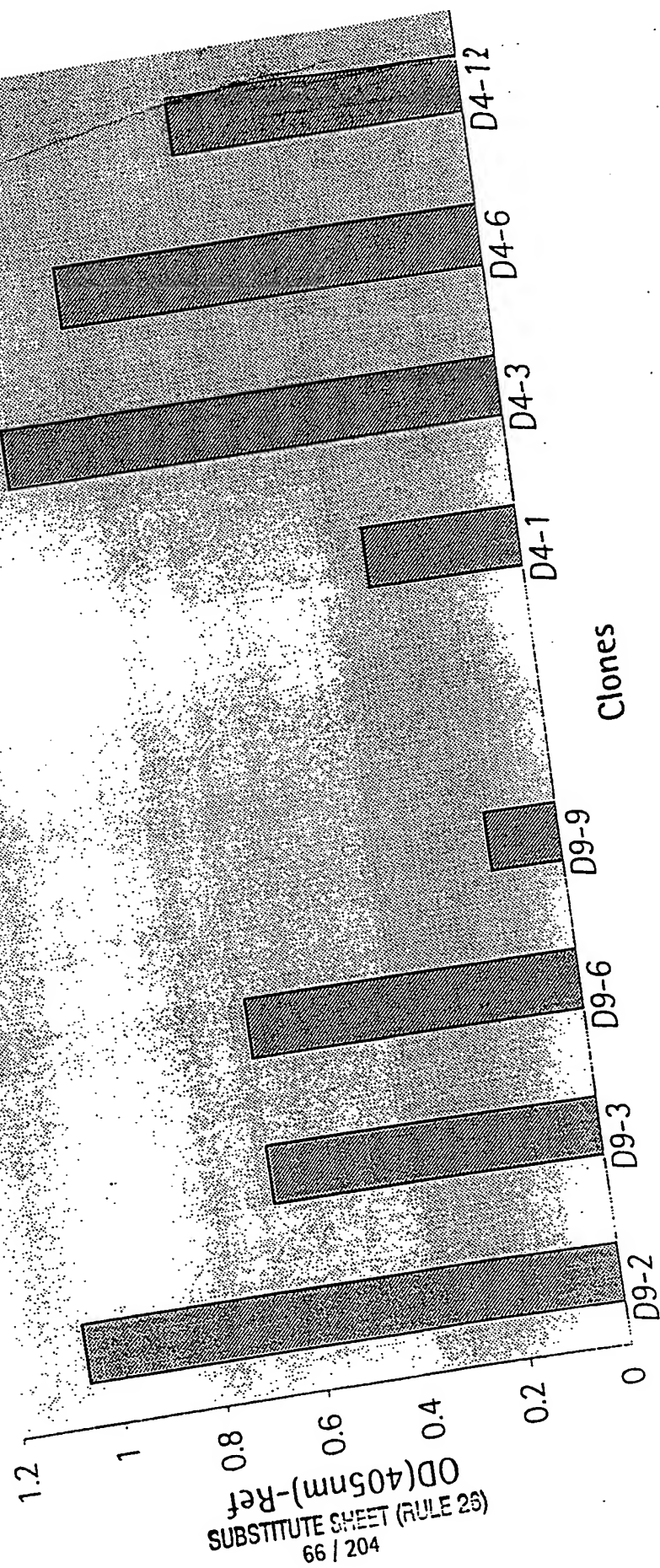


Figure 18: ELISA of anti-ESL-1 and anti- $\beta$ -estradiol antibodies

Figure 19: Selectivity and cross-reactivity of HuCAL antibodies

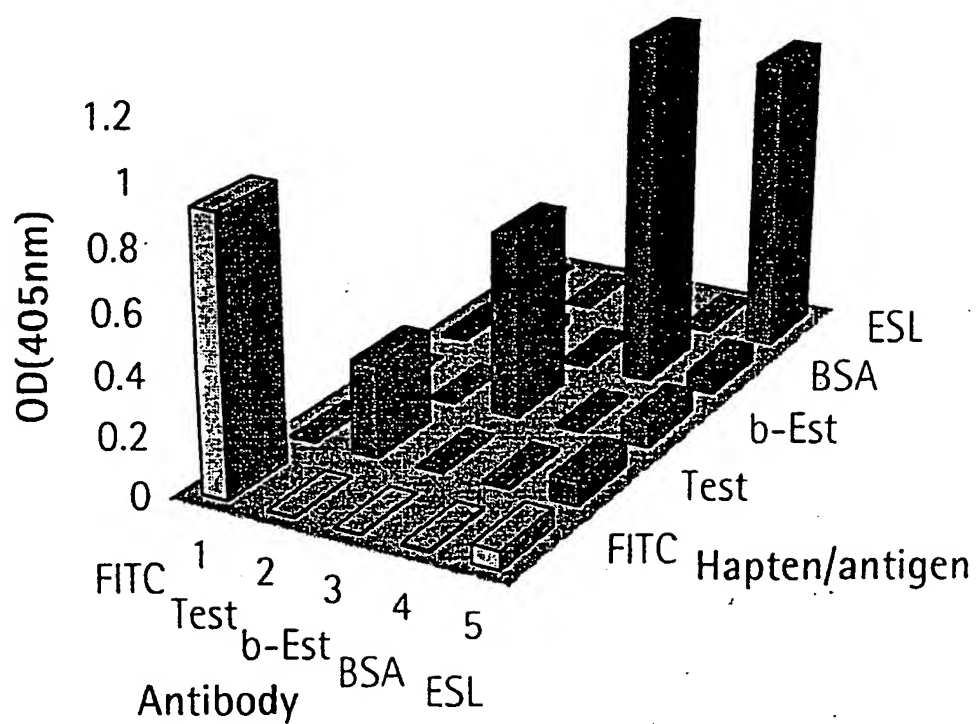






Figure 21: Sequence analysis of testosterone binders

| Frequency |   |
|-----------|---|
| 4         | W |
| 3         | W |
| 2         | W |
| 1         | W |
| 1         | W |
| 1         | W |
|           | W |
|           | Y |
|           | Y |
|           | Y |
|           | V |
|           | Y |
|           | Y |
|           | D |
|           | D |
|           | D |
|           | D |
|           | D |
|           | D |
|           | F |
|           | F |
|           | F |
|           | F |
|           | F |
|           | F |
|           | A |
|           | Q |
|           | Q |
|           | M |
|           | W |
|           | Q |
|           | L |
|           | M |
|           | M |
|           | T |
|           | K |
|           | M |
|           | K |
|           | K |
|           | K |
|           | K |
|           | M |
|           | Q |
|           | R |
|           | Q |
|           | N |
|           | M |
|           | I |
|           | R |
|           | K |
|           | W |
|           | R |
|           | S |
|           | A |
|           | A |
|           | A |
|           | A |
|           | A |
|           | R |
|           | H |
|           | Y |
|           | G |
|           | L |
|           | R |
|           | K |
|           | R |
|           | K |
|           | P |
|           | K |
|           | I |
|           | N |
|           | V |
|           | K |
|           | K |
|           | R |
|           | Y |
|           | Y |
|           | Y |
|           | Y |
|           | R |
|           | Y |
|           | R |
|           | R |
|           | R |
|           | A |
|           | A |
|           | A |
|           | A |
|           | A |
|           | A |
|           | C |
|           | C |
|           | C |
|           | C |
|           | C |
|           | C |

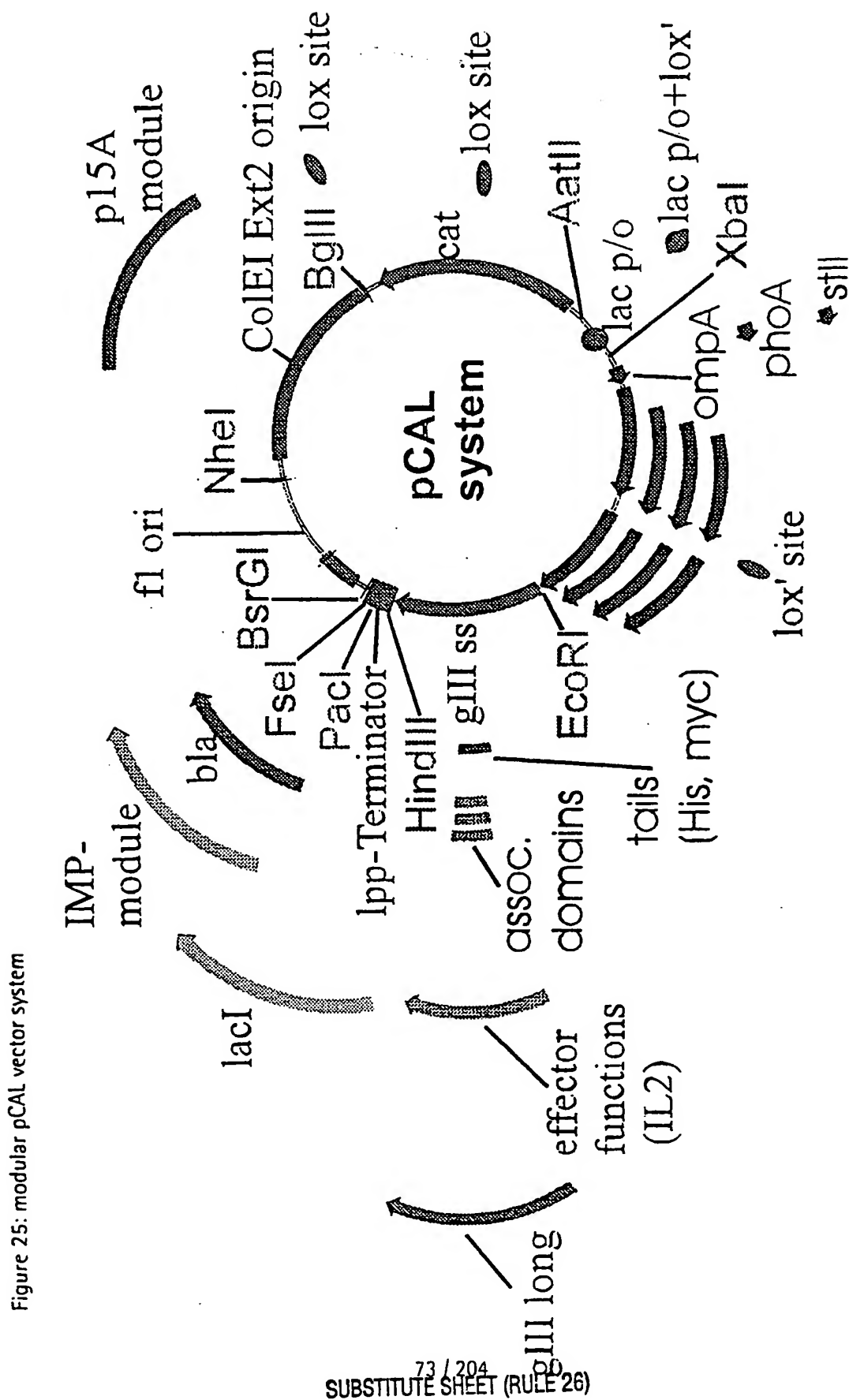




Figure 24: Sequence analysis of BSA binders

| Frequency |   |
|-----------|---|
| 5         | W |
| 1         | W |
| 1         | W |
| 1         | W |
| 1         | W |
| 1         | W |
| 1         | W |
|           | Y |
|           | V |
|           | V |
|           | Y |
|           | Y |
|           | V |
|           | D |
|           | D |
|           | D |
|           | D |
|           | D |
|           | D |
|           | M |
|           | F |
|           | M |
|           | M |
|           | M |
|           | F |
|           | V |
|           | R |
|           | R |
|           | Q |
|           | Y |
|           | F |
|           | V |
|           | S |
|           | W |
|           | H |
|           | D |
|           | Y |
|           | V |
|           | W |
|           | N |
|           | T |
|           | I |
|           | N |
|           | E |
|           | S |
|           | P |
|           | L |
|           | A |
|           | Y |
|           | M |
|           | L |
|           | A |
|           | P |
|           | Y |
|           | M |
|           | Q |
|           | R |
|           | W |
|           | K |
|           | F |
|           | Y |
|           | E |
|           | Y |
|           | R |
|           | F |
|           | G |
|           | T |
|           | F |
|           | E |
|           | S |
|           | G |
|           | Q |
|           | F |
|           | F |
|           | K |
|           | P |
|           | G |
|           | D |
|           | V |
|           | V |
|           | E |
|           | Y |
|           | D |
|           | R |
|           | R |
|           | R |
|           | R |
|           | R |
|           | R |
|           | A |
|           | A |
|           | A |
|           | A |
|           | A |
|           | A |
|           | C |
|           | C |
|           | C |
|           | C |
|           | C |
|           | C |

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Figure 25a: List of unique restriction sites used in or suitable for HuC $\Delta$ L genes or pCAL vectors

| unique restriction site | Isoschizomers                     |
|-------------------------|-----------------------------------|
| AatII                   | /                                 |
| AflII                   | Bfrr, BspTI, Bst98I               |
| AscI                    | /                                 |
| Asel                    | Vspl, AsnI, PshBI                 |
| BamHI                   | BstI                              |
| BbeI                    | EheI, KasI, NarI                  |
| BbsI                    | BpuAI, BpiI                       |
| BglII                   | /                                 |
| BlpI                    | Bpu1102I, CelII, BliI             |
| BsaBI                   | MamI, Bsh1365I, BsrBRI            |
| BsiWI                   | Pfl23II, SphI, SnuI               |
| BspEI                   | AccIII, BseAI, BsiMI, Kpn2I, MroI |
| BsrGI                   | Bsp1407I, SspBI                   |
| BssHII                  | Paul                              |
| BstEII                  | BstPI, Eco91I, EcoO65I            |
| BstXI                   | /                                 |
| Bsu36I                  | AocI, CvnI, Eco81I                |
| Drall                   | /                                 |
| DsmAI                   | BstZI, EclXI, Eco52I, XmaIII      |
| EagI                    | /                                 |
| Eco57I                  | Drall                             |
| EcoO109I                | /                                 |
| EcoRI                   | Eco32I                            |
| EcoRV                   | /                                 |
| FseI                    | /                                 |
| HindIII                 | /                                 |
| HpaI                    | Acc65I, Asp718I                   |
| KpnI                    | /                                 |
| MluI                    | BalI, MluNI                       |
| MscI                    | /                                 |

Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

| unique restriction site | Isoschizomers                      |
|-------------------------|------------------------------------|
| MunI                    | MfeI                               |
| NheI                    | /                                  |
| NsiI                    | Ppu10I, EcoT22I, Mph1103I          |
| NspV                    | Bsp119I, BstBI, Csp45I, LspI, SfuI |
| PacI                    | /                                  |
| PmeI                    | /                                  |
| PmlI                    | BbrPI, Eco72I, PmaCI               |
| Psp5II                  | PpuMI                              |
| PstI                    | /                                  |
| RsrII                   | (RsrI), CpoI, CspI                 |
| SanDI                   | /                                  |
| SapI                    | /                                  |
| SexAI                   | /                                  |
| SpeI                    | /                                  |
| SfiI                    | /                                  |
| SphI                    | BbuI, PaeI, NspI                   |
| StuI                    | AatI, Eco147I                      |
| StyI                    | Eco130I, EcoT14I                   |
| XbaI                    | BspLU11II                          |
| XhoI                    | PaeR7I                             |
| XmaI                    | AvaI, SmaI, Cfr9I, PspAI           |

Figure 26: list of pCAL vector modules

| No   | module/flanking restriction sites | functional element                                            | sites to be removed | sites to be inserted | template      | reference                                                                                                                           |
|------|-----------------------------------|---------------------------------------------------------------|---------------------|----------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------|
| M1   | AatII-lacp/o-XbaI                 | lac promoter/operator                                         | 2x VspI (AseI)      | AatII                | vector pASK30 | Skerra et al. (1991) Bio/Technology 9, 273-278                                                                                      |
| M2   | BglII-lox-AatII                   | Cre/lox recombination site                                    | 2x VspI (AseI)      | lox, BglII           | (synthetic)   | Hoess et al. (1986) Nucleic Acids Res. 2287-2300                                                                                    |
| M3   | XbaI-lox'-SphI                    | Cre/lox' recombination site                                   | none                | lox', SphI           | (synthetic)   | see M2                                                                                                                              |
| M7-I | EcoRI-glllong-HindIII             | gllp of filamentous phage with N-terminal myctail/amber codon | SphI, BamHI         | none                 | vector pIG10  | Ge et al., (1994) Expressing antibodies in E. coli. In: Antibody engineering: A practical approach. IRL Press, New York, pp 229-266 |



Figure 26: list of pCAL vector modules

|         |                      |                                                                          |                            |                   |              |          |
|---------|----------------------|--------------------------------------------------------------------------|----------------------------|-------------------|--------------|----------|
| M7-II   | EcoRI-gIIIss-HindIII | truncated gIIIp of filamentous phage with N-terminal Gly-Ser linker      | SphI                       |                   | vector pIG10 | see M7-I |
| M7-III  | EcoRI-gIIIss-HindIII | truncated gIIIp of filamentous phage with N-terminal myctail/amber codon | SphI, BbsI                 |                   | vector pIG10 | see M7-I |
| M8      | SphI-lox-HindIII     | Cre/lox recombination site                                               | none                       | lox               | (synthetic)  | see M3   |
| M9-II   | HindIII-lpp-PacI     | lpp-terminator                                                           | none                       | PacI, FseI        | (synthetic)  | see M1   |
| M10-II  | PacI/FseI-bla-BsrGI  | beta-lactamase/bla (ampR)                                                | VspI, Eco57I, BssSI        | PacI, FseI, BsrGI | pASK30       | see M1   |
| M11-II  | BsrGI-f1 ori-NheI    | origin of single-stranded replication                                    | DrallI (BanII not removed) | BsrGI, NheI       | pASK30       | see M1   |
| M11-III | BsrGI-f1 ori-NheI    | origin of single-stranded replication                                    | DrallI, BanII              | BsrGI, NheI       | pASK30       | see M1   |

Figure 26: list of pCAL vector modules

|          |                      |                                                       |                            |                   |             |                                                                  |
|----------|----------------------|-------------------------------------------------------|----------------------------|-------------------|-------------|------------------------------------------------------------------|
| M12      | NheI-p15A-BglIII     | origin of double-stranded replication                 | BssSI, VspI, NspV          | NheI, BglIII      | pACYC184    | Rose, R.E. (1988) Nucleic Acids Res. 16, 355                     |
| M13      | BglIII-lox-BglIII    | Cre/lox recombination site                            | none                       | BglIII, lox, XmnI | (synthetic) | see M3                                                           |
| M14-Ext2 | BglIII-ColEI-NheI    | origin of double-stranded replication                 | Eco57I (BssSI not removed) | BglIII, NheI      | pUC19       | Yanisch-Peron, C. (1985) Gene 33,103-119,                        |
| M17      | AatII-cat-BglIII     | chloramphenicol-acetyltransferase/cat (camR)          | BspEI, MscI, StyI/NcoI     |                   | pACYC184    | Cardoso, M. & Schwarz, S. (1992) J. Appl. Bacteriol. 72, 289-293 |
| M19      | XbaI-phoA-EcoRI      | signal sequence of phosphatase A                      | (synthetic)                |                   | (synthetic) | see M1                                                           |
| M20      | XbaI-phoA-FLAG-EcoRI | signal sequence of phosphatase A + FLAG detection tag | (synthetic)                |                   | (synthetic) | Knappik, A & Plückthun, A. (1994) BioTechniques 17, 754-761      |

Figure 26: list of pCAL vector modules

|     |                       |                                            |                                                    |  |             |                                                                               |
|-----|-----------------------|--------------------------------------------|----------------------------------------------------|--|-------------|-------------------------------------------------------------------------------|
| M21 | XbaI-stII-SapI        | heat-stable enterotoxin II signal sequence | (synthetic)                                        |  | (synthetic) | Lee et al. (1983) Infect. Immunol. 264-268                                    |
| M41 | AflII-lacI-NheI       | lac-repressor                              | BstXI, MluI, BbsI, BanII, BstEII, HpaI, BbeI, VspI |  | pASK30      | see M1                                                                        |
| M42 | EcoRI-Histail-HindIII | poly-histidine tail                        | (synthetic)                                        |  | (synthetic) | Lindner et al., (1992) Methods: a companion to methods in enzymology 4, 41-56 |

Figure 27: functional map and sequence of MCS module

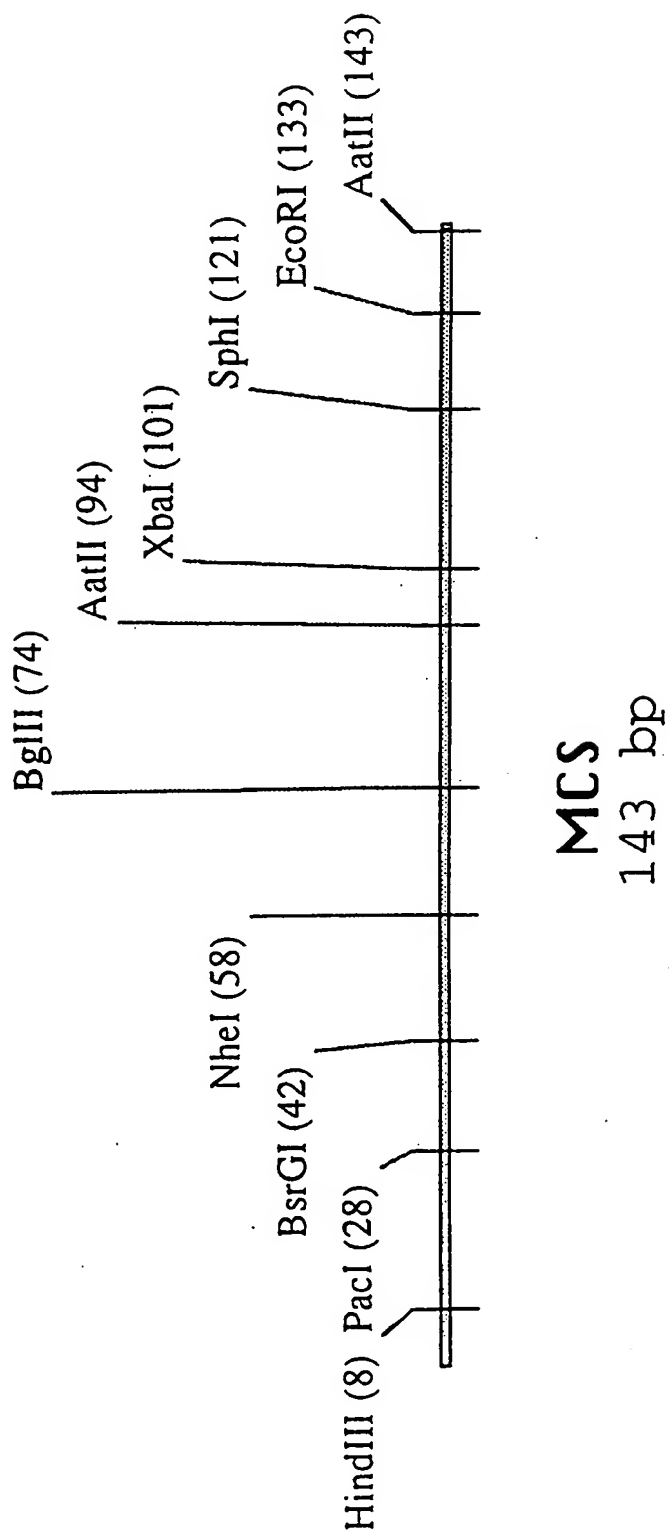


Figure 27: functional map and sequence of MCS module (continued)

|     | HindIII                                                | PacI  | BsrGI       |
|-----|--------------------------------------------------------|-------|-------------|
| 1   | ACATGTAAGC TTCCCCCCCC CCTTAATTAA CCCCCCCCCC TGTACACCCC | ~~~~~ | ~~~~~       |
|     | TGTACATTCC AAGGGGGGGG GGAATTAATT GGGGGGGGGG ACATGTGGGG |       |             |
| 51  | CCCCCGGCTA GCCCCCCCCC CCAGATCTCC CCCCCCCCCG CGTCCCCCCT | BglII | AatII XbaI  |
|     | GGGGGGCGAT CGGGGGGGGG GGTCTAGAGG GGGGGGGGCT GCAGGGGGGA | ~~~~~ | ~~~~~       |
| 101 | CTAGACCCCC CCCCCGCATG CCCCCCCCCC CGAATTCGAC GTC        | SphI  | EcoRI AatII |
|     | GATCTGGGGG GGGGGCGTAC GGGGGGGGGG GCTTAAGCTG CAG        | ~~~~~ | ~~~~~       |

Figure 28: functional map and sequence of pMCS cloning vector

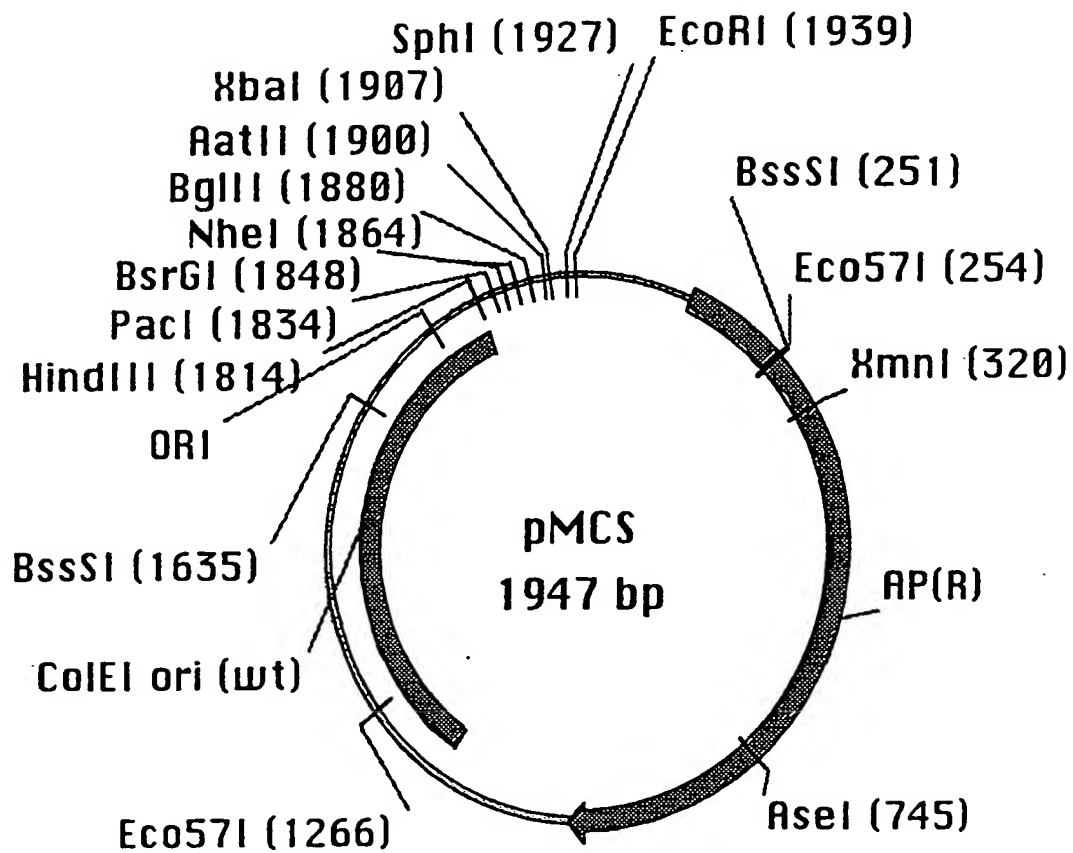


Figure 28: functional map and sequence of pMCS cloning vector (continued)

```

1 CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT TTGTTTATTT
 GTCCACCGTG AAAAGCCCTT TTACACGCGC CTTGGGGATA AACAAATAAA

51 TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCTGATA
 AAGATTATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

101 AATGCTTCAA TAAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC
 TTACGAAGTT ATTATAACTT TTTCCTTCTC ATACTCATAA GTTGTAAGG

151 GTGTCGCCCT TATTCCCCTT TTTGCGGCAT TTTGCCCTTCC TGTTTTTGCT
 CACAGCGGGA ATAAGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA

 Eco57I
                                     ~~~~~

201 CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAAGATC AGTTGGGTGC
   GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTTCTAG TCAACCCACG
                                     BssSI

251 ACGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
   TGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT
   BssSI
   ~~~~~

```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

## XmnI

```

301 GTTTTCGCC CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTCTG
 CAAAGCGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTCAAGAC

351 CTATGTGGCG CGGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG
 GATACACCGC GCCATAATAG GGCATAACTG CGGCCCGTTC TCGTTGAGCC

401 TCGCCGCATA CACTATTCTC AGAATGACTT GGTGAGTAC TCACCAGTCA
 AGCGGCGTAT GTGATAAGAG TCTTACTGAA CCAACTCATG AGTGGTCAGT

451 CAGAAAAGCA TCTTACGGAT GGCA TGACAG TAAGAGAAATT ATGCAGTGCT
 GTCCTTTCGT AGAATGCC TA CCGTACTGTC ATTCTCTTAA TACGTCACGA

501 GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT
 CGGTATTGGT ACTCACTATT GTGACGCCGG TTGAATGAAG ACTGTTGCTA

551 CGGAGGACCG AAGGAGCTAA CCGCTTTT TT GCACAACATG GGGGATCATG
 GCCTCCTGGC TTCCTCGATT GGCGAAAAA CGTGTGTGAC CCCCTAGTAC

601 TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAC
 ATTGAGCGGA ACTAGCAACC CTGGCCTCG ACTTACTTCG GTATGGTTTG

651 GACGAGCGTG ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA

```

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Figure 28: functional map and sequence of pMCS cloning vector (continued)

|      |            |            |            |              |             |
|------|------------|------------|------------|--------------|-------------|
|      | CTGCTCGCAC | TGTGGTGCTA | CGGACATCGT | TACCGTTGTT   | GCAACGCGTT  |
|      |            |            |            | AseI         |             |
|      |            |            |            | ~~~~~        |             |
| 701  | ACTATTAACT | GGCGAACTAC | TTACTCTAGC | TTCCCGGCAA   | CAATTAATAG  |
|      | TGATAATTGA | CCGCTTGATG | AATGAGATCG | AAGGGCCGTT   | GTTAATTATC  |
| 751  | ACTGGATGGA | GGCGGATAAA | GTTGCAGGAC | CAC TTC TCGG | CTCGGCCCTT  |
|      | TGACCTACCT | CCGCCATATT | CAACGTCCTG | GTGAAGACGC   | GAGCCGGGAA  |
| 801  | CCGGCTGGCT | GGTTATTGCG | TGATAAATCT | GGAGCCGGTG   | AGCGTGGGTC  |
|      | GGCCGACCGA | CCAAATAACG | ACTATTTAGA | CCTCGGCCAC   | TCGCACCCAG  |
| 851  | TCGCGGTATC | ATTGCAGCAC | TGGGGCCAGA | TGGTAAGCCC   | TCCC GTATCG |
|      | AGCGCCATAG | TAACGTCGTG | ACCCCGGTCT | ACCATTCGGG   | AGGGCATAGC  |
| 901  | TAGTTATCTA | CACGACGGGG | AGTCAGGCAA | CTATGGATGA   | ACGAAATAGA  |
|      | ATCAATAGAT | GTGCTGCCCC | TCAGTCCGTT | GATACCTACT   | TGCTTTATCT  |
| 951  | CAGATCGCTG | AGATAGGTGC | CTCACTGATT | AAGCATTGGT   | AACTGTCAGA  |
|      | GTCTAGCGAC | TCTATCCACG | GAGTGACTAA | TTCGTAACCA   | TTGACAGTCT  |
| 1001 | CCAAGTTTAC | TCATATATAC | TTTAGATTGA | TTTAAAACCT   | CATTTTAAAT  |
|      | GGTTCAAATG | AGTATATATG | AAATCTAACT | AAATTTTGAA   | GTAAAAATTA  |

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Figure 28: functional map and sequence of pMCS cloning vector (continued)

```

1051 TTAAAAGGAT CTAGGTGAAG ATCCTTTTGT ATAATCTCAT GACCAAAATC
 AATTTCCTA GATCCACTTC TAGGAAAAC TATTAGAGTA CTGGTTT TAG
1101 CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT
 GGAATTGCAC TCAAAAGCAA GGTGACTCGC AGTCTGGGGC ATCTTTTCTA
1151 CAAAGGATCT TCTTGAGATC CTTTTTCTT GCGCGTAATC TGCTGCTTGC
 GTTCCCTAGA AGAACTCTAG GAAAAAAGA CGCGCATTAG ACGACGAACG
1201 AACACAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC GGATCAAGAG
 TTTGTTTTTT TGGTGGCGAT GGTCCGCCAC AAACAACGCG CCTAGTTCTC
1251 CTACCAACTC TTTTTCGGAA GGTAAC TGC TTCAGCAGAG CGCAGATACC
 GATGGTTGAG AAAAAGGCTT CCATTGACCG AAGTCGTCTC GCGTCTATGG
 Eco57I
                                     ~~~~~
1301  AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT
      TTTATGACAG GAAGATCACA TCGGCATCAA TCCGGTGGTG AAGTCTTGA
1351  CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT
      GACATCGTGG CGGATGTATG GAGCGAGACG ATTAGGACAA TGGTCACCGA

```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

|      |             |            |             |             |            |
|------|-------------|------------|-------------|-------------|------------|
| 1401 | GCTGCCAGTG  | GCGATAAGTC | GTGTCTTACC  | GGTTGGACT   | CAAGACGATA |
|      | CGACGGTCAC  | CGCTATTACG | CACAGAATGG  | CCCAACCTGA  | GTCTGCTAT  |
| 1451 | GTTACCGGAT  | AAGGCGCAGC | GGTCGGGCTG  | AACGGGGGGT  | TCGTGCACAC |
|      | CAATGGCCCTA | TTCCGCGTCG | CCAGCCCCGAC | TTGCCCCCCA  | AGCACGTGTG |
| 1501 | AGCCCAGCTT  | GGAGCGAACG | ACCTACACCG  | AAC TGAGATA | CCTACAGCGT |
|      | TCGGGTCGAA  | CCTCGCTTGC | TGGATGTGGC  | TTGACTCTAT  | GGATGTCGCA |
| 1551 | GAGCTATGAG  | AAAGCGCCAC | GCTTCCCAGAA | GGGAGAAAGG  | CGGACAGGTA |
|      | CTCGATACTC  | TTTCGCGGTG | CGAAGGGCTT  | CCCTCTTTCC  | GCCTGTCCAT |
| 1601 | TCCGGTAAGC  | GGCAGGGTCG | GAACAGGAGA  | GCGCACGAGG  | GAGCTTCCAG |
|      | AGGCCATTTCG | CCGTCCCAGC | CTTGTCCTCT  | CGCGTGCTCC  | CTCGAAGGTC |
|      |             |            |             | BssSI       |            |
|      |             |            |             | ~~~~~       |            |
| 1651 | GGGGAACGC   | CTGGTATCTT | TATAGTCCTG  | TCGGGTTTCG  | CCACCTCTGA |
|      | CCCCTTTGGC  | GACCATAGAA | ATATCAGGAC  | AGCCCAAAGC  | GGTGGAGACT |
| 1701 | CTTGAGCGTC  | GATTTTGTG  | ATGCTCGTCA  | GGGGGGCGGA  | GCCTATGGAA |
|      | GAACTCGCAG  | CTAAAACAC  | TACGAGCAGT  | CCCCCCGCCT  | CGGATACCTT |
| 1751 | AAACGCCAGC  | AACGCGCCT  | TTTACGGTT   | CCTGGCCCTT  | TGCTGGCCCT |

ure 28: functional map

```
TTTGGCGGTCG  TTGGCGGCGG  pacI
~~~~~
HindIII
~~~~~
TTGCTCACAT  GTAAGCTTCC  CCCCCCCTT  AATTAACCCC  CCCCCCTGTA
AACGAGTGTA  CATTGGAAGG  GGGGGGGAA  TTAATTGGGG  GGGGGACAT

1801  TTGCTCACAT  GTAAGCTTCC  CCCCCCCTT  AATTAACCCC  CCCCCCTGTA
AACGAGTGTA  CATTGGAAGG  GGGGGGGAA  TTAATTGGGG  GGGGGACAT

BsrGI  NheI  BglII  AatII
~~~~~
CACCCCCCCC CCGCTAGCCC CCCCCCCCAG ATCTCCCCC CCCCACGTC
GTGGGGGGGG GCGATCGGG GGGGGGGTC TAGAGGGGG GGGCTGCAG

1851 CACCCCCCCC CCGCTAGCCC CCCCCCCCAG ATCTCCCCC CCCCACGTC
GTGGGGGGGG GCGATCGGG GGGGGGGTC TAGAGGGGG GGGCTGCAG

XbaI SphI EcoRI
~~~~~
CCCCCTCTAG  ACCCCCCCCC  CGCATGCCCC  CCCCCCCGAA  TTCACGT
GGGGGAGATC  TGGGGGGGGG  GCGTACGGGG  GGGGGGGCTT  AAGTGCA

1901  CCCCCCTCTAG  ACCCCCCCCC  CGCATGCCCC  CCCCCCCGAA  TTCACGT
GGGGGAGATC  TGGGGGGGGG  GCGTACGGGG  GGGGGGGCTT  AAGTGCA
```

Figure 29: functional map and sequence of pCAL module M1

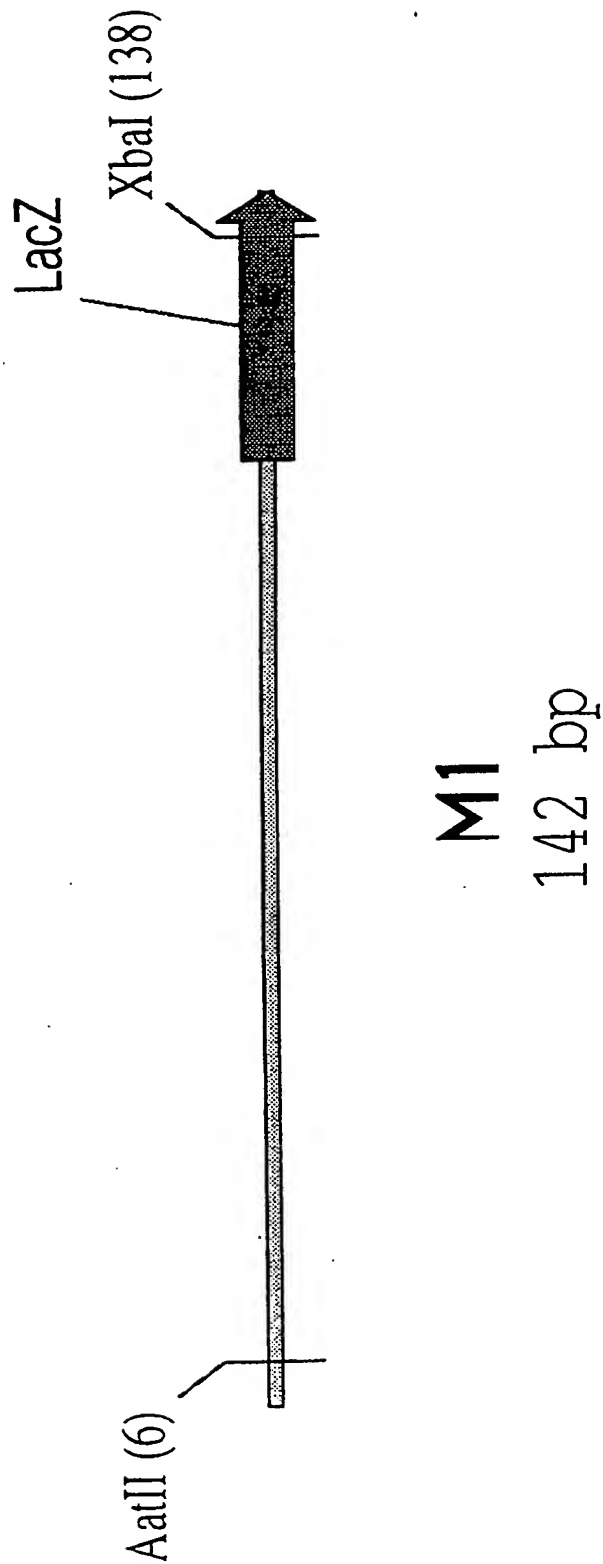
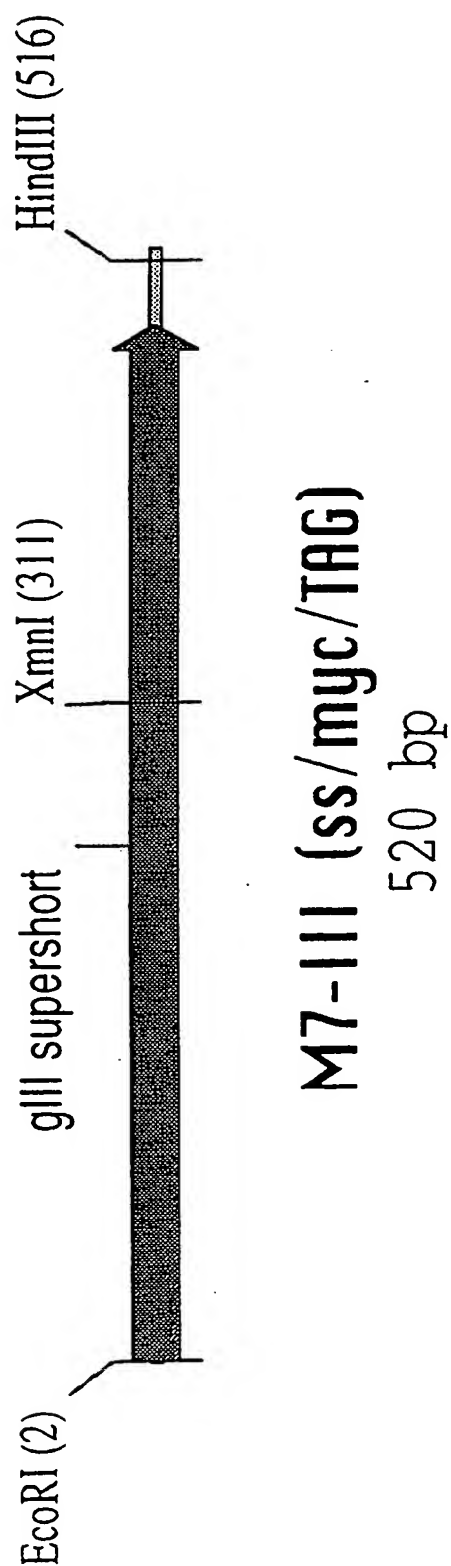


Figure 29: functional map and sequence of pCAL module M1

AatII  
 ~~~~~  
 1 GACGTCCTTAA TGTGAGTTAG CTCATCATTT AGGCACCCCA GGCTTTACAC
 CTGCAGAAATT ACACTCAATC GAGTGAGTAA TCCGTGGGGT CCGAAATGTG
 GATAACAATT
 CTATTGTTAA
 51 TTTATGCTTC CGGCTCGTAT CAACACACCT xbaI
 AAATACGAAG GCCGAGCATA ~~~~~
 101 TCACACAGGA AACAGCTATG ACCATGATTA CGAATTTCTA GA
 AGTGTGTCCT TTGTCGATAC TGGTACTAAT GCTTAAAGAT CT

Figure 30: functional map and sequence of pCAL module M7-II



ECORI

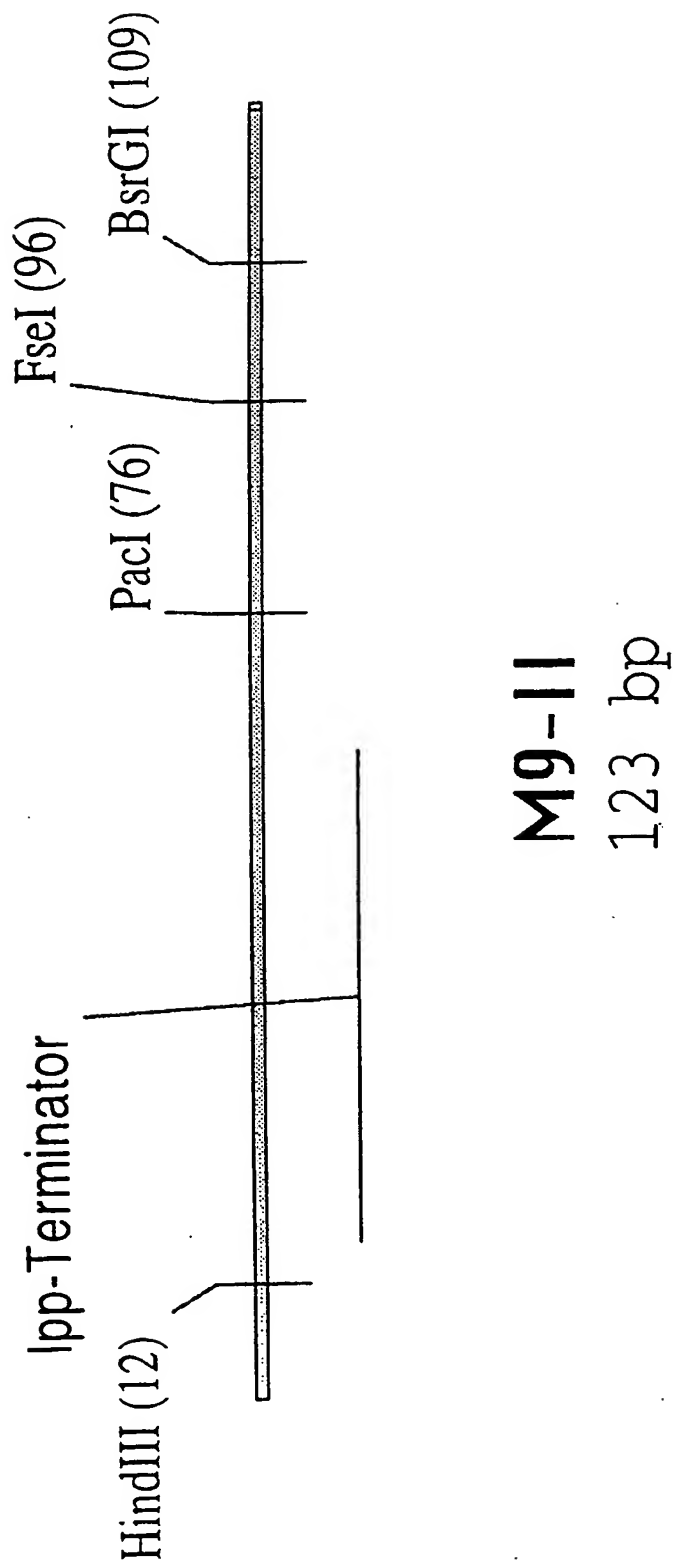
IX

Figure 30: functional map and sequence of pCAL module M7-II (continued)

351	ATGTCGCCCT	TTTGTC TTG	GCGCTGGTAA	ACCATATGAA	TTTTCTATTG
	TACAGCGGGA	AAACAGAAAC	CGCGACCAT	TGGTATACTT	AAAAGATAAC
401	ATTGTGACAA	AATAAACTTA	TTCCGTGGTG	TCTTTGCCGT	TCTTTTATAT
	TAACACTGTT	TTATTTGAAT	AAGGCACCAC	AGAAACGCAA	AGAAAATATA
451	GTTGCCACCT	TTATGTATGT	ATTTTCTACG	TTTGCTAACA	TACTGCCGTAA
	CAACGGTGGA	AATACATACA	TAAAAGATGC	AAACGATTGT	ATGACGCATT
501	TAAGGAGTCT	TGATAAGCTT			
	ATTCCCTCAGA	ACTATTTCGAA			

HindIII
~~~~~

Figure 31: functional map and sequence of pCAL module M9-II



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Figure 31: functional map and sequence of pCAL module M9-II (continued)

## HindIII

```

1  GGGGGGGGGG AAGCTTGACC TGTGAAGTGA AAAATGGCGC AGATTGTGCG
   CCCCCCCCCC TTCGAACTGG ACACTTCACT TTTTACCGCG TCTAACACGC

```

## PacI

## FseI

```

51  ACATTTTTT TGTCTGCCGT TTAATTAAG GGGGGGGGGG GCCGGCCTGG
   TGTAAAAAAA ACAGACGGCA AATAATTTC CCCCCCCCCC CGGCCGGACC

```

## BsrGI

```

101 GGGGGGGTGT ACAGGGGGG GGG
    CCCCCCACA TGTCCCCCCC CCC

```

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Figure 32: functional map and sequence of pCAL module M11-III

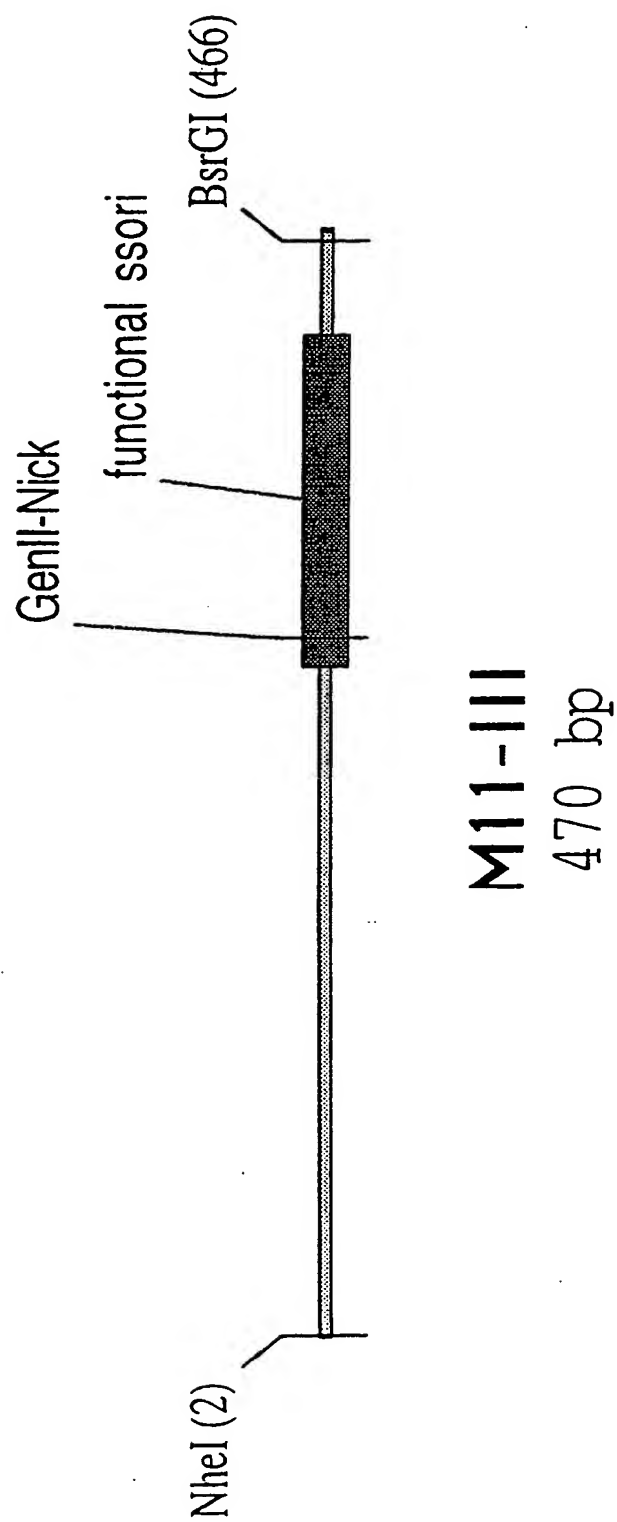


Figure 32: functional map and sequence of pCAL module M11-III (continued)

NheI  
~~~~~

1	GCTAGCACGC	GCCCTGTAGC	GGCGCATTA	GCGCGCGGG	TGTGGTGGTT
	CGATCGTGCG	CGGACATCG	CCGCGTAATT	C	ACACCACCAA
51	ACGCGCAGCG	TGACCGCTAC	ACTTGCCAGC	GCCCTAGCGC	CCGCTCCTTT
	TGCGCGTCCG	ACTGGCGATG	TGAACGGTCG	C	GGCGAGGAAA
101	CGCTTTCTTC	CCTTCCTTTC	TCGCCACGTT	C	CCCCGTCAAG
	GCGAAAGAAG	GGAAGGAAAG	AGCGGTGCAA	G	GGGCAGTTC
151	CTCTAAATCG	GGGCATCCCT	TTAGGGTTCC	GATTAGTGC	TTACGGCAC
	GAGATTTAGC	CCCGTAGGGA	AATCCCAAGG	CTAAATCAGC	AAATGCCCGTG
201	CTCGACCCCA	AAAAACTTGA	TTAGGGTGAT	GGTTCTCGTA	GTGGGCCATC
	GAGCTGGGGT	TTTTTTGAACT	AATCCCACTA	CCAAGAGCAT	CACCCGGTAG
251	GCCCTGATAG	ACGGTTTTC	GCCCTTTGAC	GTTGGAGTCC	ACGTTCTTTA
	CGGACTATC	TGCCAAAAAG	CGGAAACTG	CAACCTCAGG	TGCAAGAAAT
301	ATAGTGGACT	CTTGTTCCAA	ACTGGAACAA	CACTCAACCC	TATCTCGGTC
	TATCACCTGA	GAACAAGGTT	TGACCTTGTT	GTGAGTTGGG	ATAGAGCCAG
351	TATTCTTTTG	ATTTATAAGG	GATTTTGCCG	ATTTCGGCCT	ATTGGTTAAA

Figure 32: functional map and sequence of pCAL module M11-III (continued)

ATAAGAAAAC TAAATATTCC CTAAACCGC TAAAGCCGA TAACCAATTT

401 AAATGAGCTG ATTTAACAAA AATTAAACGC GAATTTTAAC AAAATATTAA
TTTACTCGAC TAAATTGTTT TTAAATTGCG CTTAAAATTG TTTTATAATT

BsrGI

~~~~~

451 CGTTTACAAT TTCATGTACA  
GCAAAATGTTA AAGTACATGT

Figure 33: functional map and sequence of pCAL module M14-Ext2

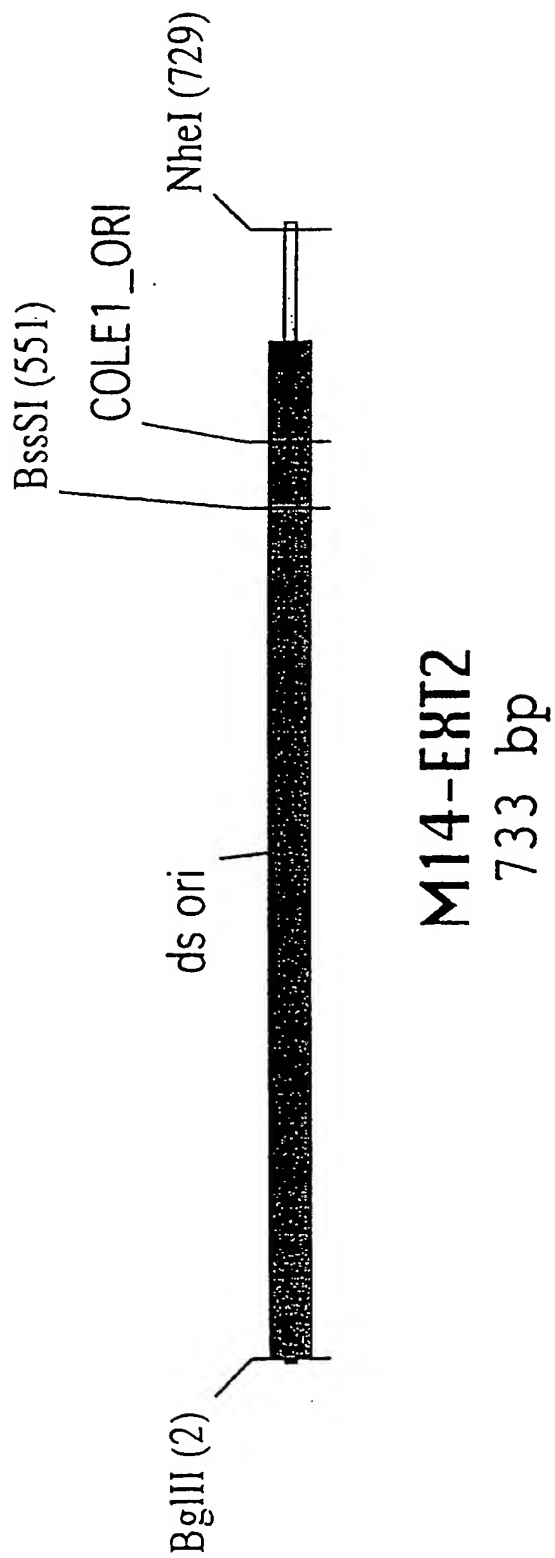


Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

## Bg1II

~~~~~

1	AGATCTGACC	AAAATCCCCTT	AACGTGAGTT	TTCGTTCCAC	TGAGCGTCAG
	TCTAGACTGG	TTTTTAGGGAA	TTGCACTCAA	AAGCAAGGTG	ACTCGCAGTC
51	ACCCCGTAGA	AAAGATCAAA	GGATCTTCTT	GAGATCCTTT	TTTCTGCGC
	TGGGGCATCT	TTTCTAGTTT	CCTAGAAGAA	CTCTAGGAAA	AAAAGACGCG
101	GTAATCTGCT	GCTTGCAAAC	AAAAAAACCA	CCGCTACCAG	CGGTGGTTTG
	CATTAGACGA	CGAACGTTTG	TTTTTTTGGT	GCGATGGTC	GCCACCAAAC
151	TTTGCCGGAT	CAAGAGCTAC	CAACTCTTTT	TCCGAAGGTA	ACTGGCTACA
	AAACGGCCTA	GTTCCTCGATG	GTGAGAAAA	AGGCTTCCAT	TGACCGATGT
201	GCAGAGCGCA	GATACCAAAT	ACTGTTCTTC	TAGTGTAGCC	GTAGTTAGGC
	CGTCTCGCGT	CTATGGTTTA	TGACAAGAAG	ATCACATCGG	CATCAATCCG
251	CACCACTTCA	AGAACTCTGT	AGCACCCGCT	ACATACCTCG	CTCTGCTAAT
	GTGGTGAAAGT	TCTTGAGACA	TCGTGGCGGA	TGTATGGAGC	GAGACGATTA
301	CCTGTTACCA	GTGGCTGCTG	CCAGTGCGGA	TAAGTCGTGT	CTTACCGGGT
	GGACAATGGT	CACCGACGAC	GGTCACCGCT	ATTCAGCACA	GAATGGCCCA
351	TGGACTCAAG	ACGATAGTTA	CCGGATAAGG	CGCAGCGGTC	GGGCTGAACG

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

```

      ACCTGAGTTC TGCTATCAAT GGCCTATTCC GCGTCGCCAG CCCGACTTGC
401  GGGGGTTCGT GCACACAGCC CAGCTTGGAG CGAACGACCT ACACCGAACT
      CCCCCAAGCA CGTGCTCGG GTCGAACCTC GCTTGCTGGA TGTGGCTTGA
451  GAGATACCTA CAGCGTGAGC TATGAGAAAG CGCCACGCTT CCCGAAGGGA
      CTCTATGGAT GTCGCACCTCG ATACTCTTTC GCGGTGCCGA GGGCTTCCCT
501  GAAAGGCGGA CAGGTATCCG GTAAGCGGCA GGTTCGGAAC AGGAGAGCGC
      CTTTCCGCCT GTCCATAGGC CATTCGCCGT CCCAGCCTTG TCCTCTCGCG
      BssSI
      ~~~~~
551  ACGAGGGAGC TTCCAGGGGG AAACGCCCTGG TATCTTTATA GTCCGTGTCGG
      TGCTCCCTCG AAGGTCCCCC TTTCGGGACC ATAGAAATAT CAGGACAGCC
      BssSI
      ~~~~~
601  GTTTCGCCAC CTCTGACTTG AGCGTCGATT TTTGTGATGC TCGTCAGGGG
      CAAAGCGGTG GAGACTGAAC TCGCAGCTAA AACACTACG AGCAGTCCCC
651  GCGGAGCCT ATGGAAAAC GCCAGCAACG CGGCCCTTTT ACGGTTCCTG
      CCGCCTCGGA TACCTTTTTC CGGTCGTTGC GCCGGAAAAA TGCCAAGGAC

```

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

		NheI
701	GCCTTTTGCT GGCCTTTTGC TCACATGGCT AGC	~~~~~
	CGGAAAACGA CCGGAAAACG AGTGTAACCGA TCG	

Figure 34: functional map and sequence of pCAL module M17

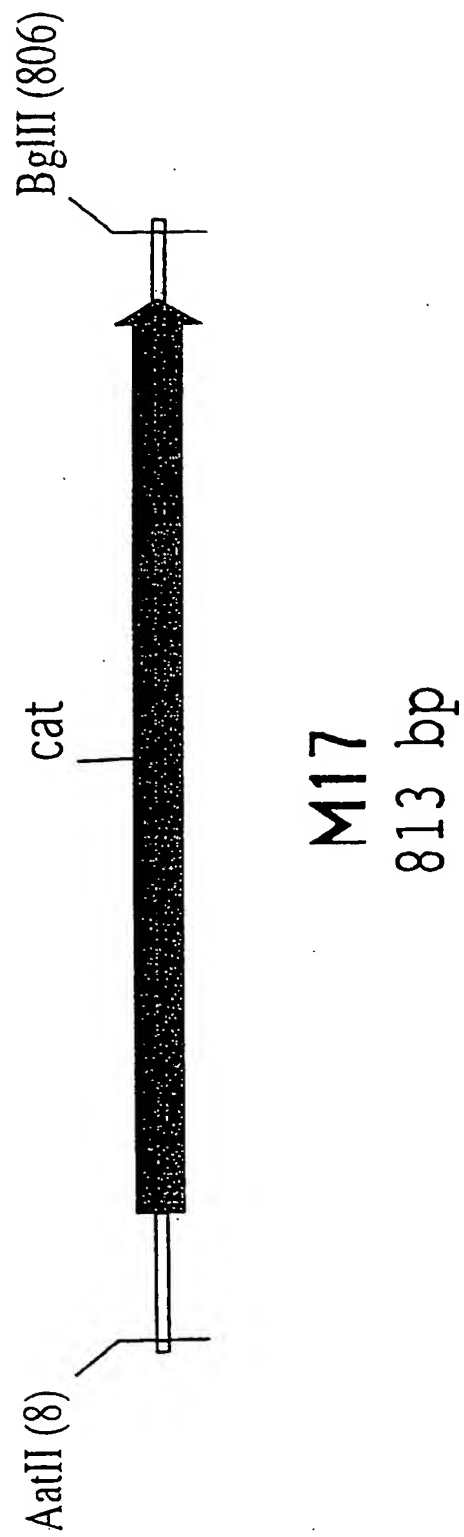


Figure 34: functional map and sequence of pCAL module M17. (continued)

AatII
~~~~~

|     |             |              |             |             |              |
|-----|-------------|--------------|-------------|-------------|--------------|
| 1   | GGGACGTCGG  | GTGAGGTTCC   | AAC TT CACC | ATAATGAAAT  | AAGATCACTA   |
|     | CCCTGCAGCC  | CACTCCAAGG   | TTGAAAGTGG  | TAT TACTTTA | TTCTAGTGAT   |
| 51  | CCGGGCGTAT  | TTTTTTGAGTT  | ATCGAGATTT  | TCAGGAGCTA  | AGGAAGCTAA   |
|     | GGCCCCGCATA | AAAAACTCAA   | TAGCTCTAAA  | AGTCCCTCGAT | TCCTTTCGATT  |
| 101 | AATGGAGAAA  | AAATCACTG    | GATATACCAC  | CGTTGATATA  | TCCCAATGGC   |
|     | TTACCTCTTT  | TTTTAGTGAC   | CTATATGGTG  | GCAACTATAT  | AGGGTTACCG   |
| 151 | ATCGTAAAGA  | ACATTTTGAG   | GCATTT CAGT | CAGTTGCTCA  | ATGTACCTAT   |
|     | TAGCATTTCT  | TGTA AA ACTC | CGTAAAGTCA  | GTCAACGAGT  | TACATGGATA   |
| 201 | AACCAGACCG  | TTCAGCTGGA   | TATTACGGCC  | TTTTTTAAAGA | CCGTAAAGAA   |
|     | TTGGTCTGGC  | AAGTCGACCT   | ATAATGCCCG  | AAAAAATTCTT | GGCATTTCTT   |
| 251 | AAATAAGCAC  | AAGTTT TATC  | CGGCCTTTAT  | TCACATTCTT  | GCCCCGCCCTGA |
|     | TTTATTCGTG  | TTCAAAAATAG  | GCCGGAAATA  | AGTGTAAGAA  | CGGGCGGACT   |
| 301 | TGAATGCTCA  | CCCCGAGTTC   | CGTATGGCAA  | TGAAAGACGG  | TGAGCTGGTG   |
|     | ACTTACGAGT  | GGGCCCTCAAG  | GCATACCGTT  | ACTTCTGCC   | ACTCGACCAC   |
| 351 | ATATGGGATA  | GTGTTACACC   | TTGTTACACC  | GTTTTC CATG | AGCAA ACTGA  |

Figure 34: functional map and sequence of pCAL module M17 (continued)

|     |             |            |            |             |             |
|-----|-------------|------------|------------|-------------|-------------|
|     | TATACCCCTAT | CACAAGTGGG | AACAATGTGG | CAAAAGGTAC  | TCGTTTGACT  |
| 401 | AACGTTTTC   | TCGCTCTGGA | GTGAATACCA | CGACGATTTC  | CGGCAGTTTC  |
|     | TTGCCAAAAGT | AGCGAGACCT | CACTTATGGT | GCTGCTAAAG  | GCCGTCAAAG  |
| 451 | TACACATATA  | TTCGCAAGAT | GTGGCGTGT  | ACGGTGAAA   | CCTGGCCTAT  |
|     | ATGTGTATAT  | AAGCGTTCTA | CACCGCACAA | TGCCACTTTT  | GGACCGGATA  |
| 501 | TTCCCTAAAG  | GGTTATTGA  | GAATATGTTT | TTCGTCTCAG  | CCAATCCCCTG |
|     | AAGGATTTC   | CCAAATAACT | CTTATACAAA | AAGCAGAGTC  | GGTAGGGAC   |
| 551 | GGTGAGTTTC  | ACCAGTTTTC | ATTAAACGT  | AGCCAAATATG | GACAACTTCT  |
|     | CCACTCAAAG  | TGGTCAAAAC | TAAATTGCA  | TCGGTTATAC  | CTGTTGAAGA  |
| 601 | TCGCCCCCGT  | TTTCACTATG | GGCAAATATT | ATACGCAAGG  | CGACAAGGTG  |
|     | AGCGGGGGCA  | AAAGTGATAC | CCGTTTATAA | TATGCGTTCC  | GCTGTTCCAC  |
| 651 | CTGATGCCGC  | TGGCGATTCA | GGTTCATCAT | GCCGTTTG TG | ATGGCTTCCA  |
|     | GACTACGGCG  | ACCGCTAAGT | CCAAGTAGTA | CGGCAAAACAC | TACCGAAGGT  |
| 701 | TGTCGGCAGA  | ATGCTTAATG | AATTACAACA | GTA CTGCGAT | GAGTGGCAGG  |
|     | ACAGCCGTCT  | TACGAATTAC | TTAATGTTGT | CATGACGCTA  | CTCACCGTCC  |
| 751 | GCGGGGCGTA  | ATTTTTTTAA | GGCAGTTATT | GGGTGCCCTT  | AAACGCCCTGG |

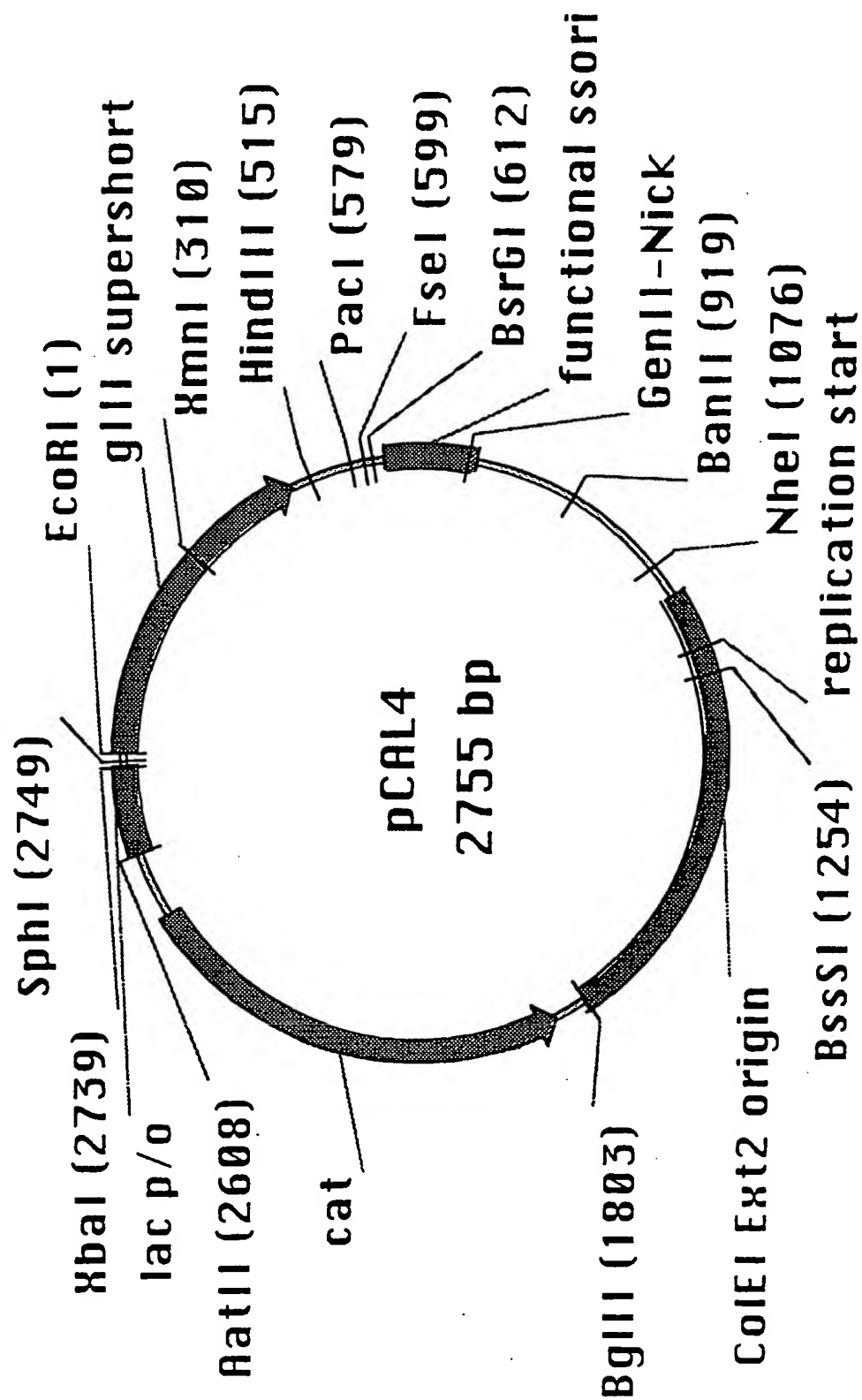
Figure 34: functional map and sequence of pCAL module M17 (continued)

CGCCCCGCGCAT TAAAAAATT CCGTCAATAA CCCACGGGAA TTGCGGACC

BglII  
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801 TGCTAGATCT TCC
ACGATCTAGA AGG

Figure 35: functional map and sequence of modular vector pCAL4



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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

ECORI			
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1	AATTCGAGCA TTAAGCTCGT	GAAGCTGATC CTTCGACTAG	TCTGAGGAGG AGACTCCTCC
51	GGTTCGGTG CCAAGGCCAC	ATTTTGATTA TAAAACTAAT	TGAAAAGATG ACTTTTCTAC
101	TATGACCGAA ATACTGGCTT	AATGCCGATG TTACGGGCTAC	AAAACCGCCT TTTTTGGCGGA
151	AACTTGATTC TTGAACCTAAG	TGTCGCTACT ACAGCGATGA	GATTACGGTG CTAATGCCAC
201	GGTGACGTTT CCACTGCATAA	CCGGCCCTTGC GGCCGGAACG	TAATGGTAAT ATTACCATT
251	TGGCTCTAAT ACCGAGATTA	TCCCAAATGG AGGGTTTACC	CTCAAGTCGG GAGTTCAGCC
		TGACGGTGAT ACTGCCACTA	
		AATTCACCCTT TTAAGTGGAA	
		XmnI	
		~~~~~	
301	TAATGAATAA ATTACTTATT	TTTCCCGTCAA AAAGGCAGTT	TATTACCTT ATAAATGGAA
		CCCTCCCTCA GGGAGGGAGT	
		ATCGGTTGAA TAGCCAACTT	

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

351	TGTCGCCCTT	TTGTCTTTGG	CGCTGGTAA	CCATATGAAT	TTTCTATTGA
	ACAGCGGGAA	AACAGAAACC	CGGACCATTT	GGTATACTTA	AAAGATAACT
401	TTGTGACAAA	ATAAACTTAT	TCCGTGGTGT	CTTTGCCGTTT	CTTTTATATG
	AACACTGTTT	TATTTGAATA	AGGCACCACA	GAAACGCCAA	GAAAATATAC
451	TTGCCACCTT	TATGTATGTA	TTTTCTACGT	TTGCTAACAT	ACTGCGTAAT
	AACGGTGGAA	ATACATACAT	AAAAGATGCA	AACGATTGTA	TGACGCATTA
HindIII					
	~~~~~				
501	AAGGAGTCTT	GATAAGCTTG	ACCTGTGAAG	TGAAAAATGG	CGCAGATTGT
	TTCCCTCAGAA	CTATTCGAAC	TGGACACTTC	ACTTTTTACC	CGGTCTAACA
PacI					
	~~~~~				
551	GGGACATTTT	TTTTGTCTGC	CGTTTAATTA	AAGGGGGGGG	GGGGCCGGCC
	CGCTGTAAAA	AAAACAGACG	GCAAATTAAT	TTCCCCCCCC	CCCCGGCCGG
BsrGI					
	~~~~~				
601	TGGGGGGGGG	TGTACATGAA	ATTGTAAACG	TTAATATTTT	GTTAAAATTC
	ACCCCCCCCC	ACATGTACTT	TAACATTTTC	AATTATAAAA	CAATTTTAAG

08320

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

651	CGGTTAAATT CGCAATTAA	TTTGTTAAAT AAACAATTAA	CAGCTCATTT GTCGAGTAAA	TTTAACCAAT AAATTGGTTA	AGGCCGAAAT TCCGGCTTTA
701	CGGCAAAATC GCCGTTTATG	CCTTATAAAT GGAATATTTA	CAAAGAATA GTTTCTTAT	GACCGAGATA CTGGCTCTAT	GGGTTGAGTG CCCAACTCAC
751	TTGTTCCAGT AACAAAGTCA	TTGGAACAAG AACCTTGTTT	AGTCCACTAT TCAGGTGATA	TAAAGAACGT ATTCTTGCA	GACTCCAAC CCTGAGGTTG
801	GTCAAAAGGC CAGTTTCCCG	GAAAACCGT CTTTTGGCA	CTATCAGGC GATAGTCCCG	GATGGCCAC CTACCGGTG	TACGAGAAC ATGCTCTTG
851	ATCACCCCTAA TAGTGGGATT	TCAAGTTTTT AGTTCAAAA	TGGGTCGAG ACCCAGCTC	GTGCCGTAA CACGGCATTT	GCACTAAATC CGTGATTTAG
901	GGAACCCCTAA CCTTGGGATT	AGGAGCCCC TCCCTCGGG	CGATTAGAG GCTAAATCTC	CTTGACGGG GAACTGCCCC	AAAGCCGGCG TTTCGGCCCG
951	AACGTGGCGA TTGCACCGCT	GAAAGGAAG CTTTCCTTCC	GAAGAAAGC CTTCTTTCCG	AAAGAGCGG TTTCCTCGCC	GCGCTAGGGC CGCGATCCCC

BanII

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1001 GCTGGCAAGT GTAGCGGTCA CGCTGGCGGT AACCAACACA CCGCGCGCGC
CGACCGTTCA CATCGCCAGT GCGACGCGCA TTGGTGGTGT GGGCGGCGCG

NheI

}
}
}
}
}
}

1051 TTAATGCGCC GCTACAGGC GCGTGCTAGC CATGTGAGCA AAAGGCCAGC
AATTACGCGG CGATGTCCCG CGCACGATCG GTACACTCGT TTTCGGTCTG

1101 AAAAGGCCAG GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCATAGG
TTTTCGGTC CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC

1151 CTCCGCCCCC CTGACGAGCA TCACAAAAT CGACGCTCAA GTCAGAGGTG
GAGGCGGGGG GACTGCTCGT AGTGTTTTA GCTGCGAGTT CAGTCTCCAC

11201 GCGAAACCCG ACAGGACTAT AAAGATACCA GCGTTTCCC CCTGGAAGCT
CGCTTTGGGC TGTCCTGATA TTTCATAGGT CCGCAAAGGG GGACCTTCCA

BSI

2
2
2
2
2
2

11251
CCCTCGTGG CTCTCCTGTT CCGACCCCTGC CGCTTACCGG ATACCTGTCC
GGAGCACGC GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG

11301 GCCTTTCTCC CTTGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG
CGGAAAGAGG GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

| | | | | | |
|------|-------------|-------------|-------------|------------|-------------|
| 1351 | GTATCTCAGT | TCGGTGTAGG | TCGTTTCGCTC | CAAGCTGGGC | TGTGTGCACG |
| | CATAGAGTCA | AGCCACATCC | AGCAAGCGAG | GTTCGACCCG | ACACACGTGC |
| 1401 | AACCCCCCGT | TCAGCCCCGAC | CGCTGCGCCT | TATCCGGTAA | CTATCGTCTT |
| | TTGGGGGGCA | AGTCGGGCTG | GCGACGCGGA | ATAGGCCATT | GATAGCAGAA |
| 1451 | GAGTCCAACC | CGGTAAGACA | CGACTTATCG | CCACTGGCAG | CAGCCACTGG |
| | CTCAGGTTGG | GCCATTCTGT | GCTGAATAGC | GTGACCCGTC | GTGCGTGACC |
| 1501 | TAACAGGATT | AGCAGAGCGA | GGTATGTAGG | CGGTGCTACA | GAGTTCTTGA |
| | ATTGTCCTAA | TCGTCTCGCT | CCATACATCC | GCCACGATGT | CTCAAGAACT |
| 1551 | AGTGGTGCGC | TAACTACGGC | TACACTAGAA | GAACAGTATT | TGGTATCTGC |
| | TCACCAACCGG | ATTGATGCCG | ATGTGATCTT | CTTGTCATAA | ACCATAGACG |
| 1601 | GCTCTGCTGT | AGCCAGTTAC | CTTCGGAAAA | AGAGTTGGTA | GCTCTTGATC |
| | CGAGACGACA | TCGGTCAATG | GAAGCCCTTTT | TCTCAACCAT | CGAGAACTAG |
| 1651 | CGGCAAAACA | ACCACCGCTG | GTAGCGGTGG | TTTTTTTGT | TGCAAGCAGC |
| | GCCGTTTGTT | TGGTGGCGAC | CATCGCCACC | AAAAAAACAA | ACGTTCTGTCG |
| 1701 | AGATTACGCG | CAGAAAAAAA | GGATCTCAAG | AAGATCCCTT | GATCTTTTCT |
| | TCTAATGCGC | GTCTTTTTTT | CCTAGAGTTC | TTCTAGGAAA | CTAGAAAAAG |

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

1751 ACGGGGCTCTG ACGCTCAGTG GAACGAAAC TCACGTTAAG GGATTTTGGT
TGCCCCAGAC TGCAGATCAC CTTGCTTTTG AGTGCAATTC CTAATAACCA

BglII
~~~~~

1801 CAGATCTAGC ACCAGGCGTT TAAGGCACCC AATAACTGCC TTAAAAAAT  
GTCTAGATCG TGGTCCGCAA ATTCCCCTGG TTATTGACGG AATTTTTTTA

1851 TACGCCCCCGC CCTGCCACTC ATCGCAGTAC TGTTGTAATT CATTAAGCAT  
ATGCGGGGCG GGACGGTGAG TAGCGTCATG ACAACATTAA GTAATTTCGTA

1901 TCTGCCGACA TGGAGCCAT CACAACGGC ATGATGAACC TGAATCGCCA  
AGACGGCTGT ACCTTCGGTA GTGTTTGCCG TACTACTTGG ACTTAGCGGT

1951 GCGGCATCAG CACCTTGTCG CCTTGCGTAT AATATTGCCC CATAGTGAAA  
CGCCGTAGTC GTGGAACAGC GGAACGCATA TTATAAACGG GTATCACTTT

2001 ACGGGGGCGA AGAAGTTGTC CATAATGGCT ACGTTTAAAT CAAAACGTGT  
TGCCCCCGCT TCTTCAACAG GTATAACCGA TGCAAAATTA GTTTTGACCA

2051 GAAACTCACC CAGGATTGG CTGAGACGAA AAACATATTC TCAATAAACCC  
CTTTGAGTGG GTCCCTAACC GACTCTGCTT TTTGTATAAG AGTTATTG

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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

2101	CTTTAGGAA ATAGGCCAGG TTTTCACCGT AACACGCCAC ATCTTGCGAA	TGTTGCGGTG TAGAACGCTT
	GAAATCCCTT TATCCGGTCC AAAAGTGGCA	
2151	TATATGTGTA GAAACTGCCG GAAATCGTCG TGGTATTCAC TCCAGAGCGA	AGGTCTCGCT
	ATATACACAT CTTTGACGGC CTTAGCAGC ACCATAAGTG	
2201	TGAAAACGTT TCAGTTTGCT CATGGAAAC GGTGTAACAA GGTGAACAC	CCCAC TTGTG
	ACTTTTGCAA AGTCAAACGA GTACCTTTTG CCACATTGTT	
2251	TATCCCATAT CACAGCTCA CCGTCTTTCA TTGCCATACG GAACTCCGGG	CTTGAGGCC
	ATAGGGTATA GTGGTCGAGT GGCAGAAAGT AACGGTATGC	
2301	TGAGCATTCA TCAGCGGGC AAGAATGTGA ATAAAGGCCG GATAAACTT	CTATTTTGAA
	ACTCGTAAGT AGTCCGCCCG TTCTTACACT TATTTCCGGC	
2351	GTGCTTATTT TTCTTTACGG TCCTTAAAAA GGCCGTAATA TCCAGCTGAA	AGGTCCGACTT
	CACGAATAAA AAGAAATGCC AGAAATTTT CCGCATTTAT	
2401	CGGCTCTGGTT ATAGGTACAT TGAGCAACTG ACTGAAATGC CTCAAAATGT	GAGTTTACA
	GCCAGACCAA TATCCATGTA ACTCGTTGAC TGACTTTACG	
2451	TCCTTACGAT GCCATTGGGA TATATCAACG GTGGTATATC CAGTGATTTT	GTCAC TAAAA
	AGAAATGCTA CGGTAACCCT ATATAGTTGC CACCATATAG	

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

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2501 TTTCTCCATT TTAGCTTCCT TAGCTCCTGA AAATCTCGAT AACTCAAAAA
    AAAGAGGTAA AATCGAAGGA ATCGAGGACT TTTAGAGCTA TTGAGTTTIT

2551 ATACGCCCGG TAGTGATCTT ATTTCAATTAT GGTGAAAGTT GGAACCTCAC
    TATGCGGGCC ATCACTAGAA TAAAGTAATA CCACTTTCAA CTTGGAGTG

                AatII
                ~~~~~
2601 CCGACGTCTA ATGTGAGTTA GCTCACTCAT TAGGCACCCC AGGCTTTACA
 GGCTGCAGAT TACACTCAAT CGAGTGAGTA ATCCGTGGGG TCCGAAATGT

2651 CTTTATGCTT CCGGCTCGTA TGTTGTGTGG AATTGTGAGC GGATAACAAT
 GAAATACGAA GGCCGAGCAT ACAACACACC TTAACACTCG CTAATTGTTA

 XbaI SphI
                ~~~~~
2701 TTCACACAGG AAACAGCTAT GACCATGATT ACGAATTTC T AGAGCATGCG
    AAGTGTGTCC TTTGTGCGATA CTGGTACTAA TGCTTAAAGA TCTCGTACGC

                EcoRI

2751 GGGGG
    CCCCC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors

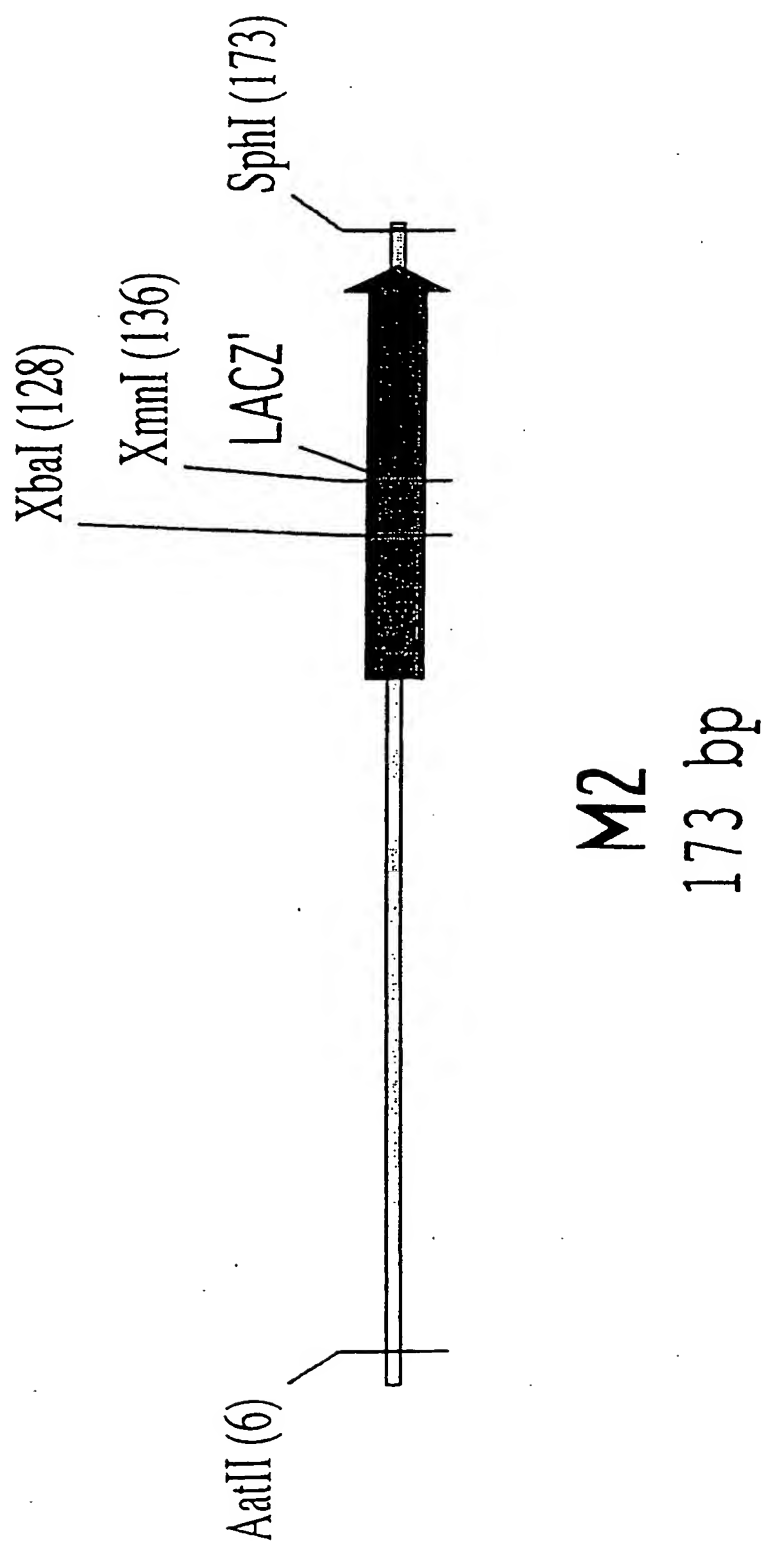




Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 2:

	AatII			
	~~~~~			
1	GACGTCCTTAA	TGTGAGTTAG	CTCACTCATT	AGGCACCCCA GGCTTTACAC
	CTGCAGAATT	ACACTCAATC	GAGTGAGTAA	TCCGTGGGGT CCGAAATGTG
51	TTTATGCTTC	CGGCTCGTAT	GTTGTGTGGA	ATTGTGAGCG GATAACAATT
	AAATACGAAG	GCCGAGCATA	CAACACACCT	TAACACTCGC CTATTGTTAA
			XmnI	~~~~~
			XbaI	~~~~~
101	TCACACAGGA	AACAGCTATG	ACCATGTCTA	GAATAACTTC GTATAATGTA
	AGTGTGTCCT	TTGTCGATAC	TGGTACAGAT	CTTATTGAAG CATATTACAT
			SphI	~~~~~
151	CGCTATACGA	AGTTATCGCA	TGC	
	GCGATATGCT	TCAATAGCGT	ACG	

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

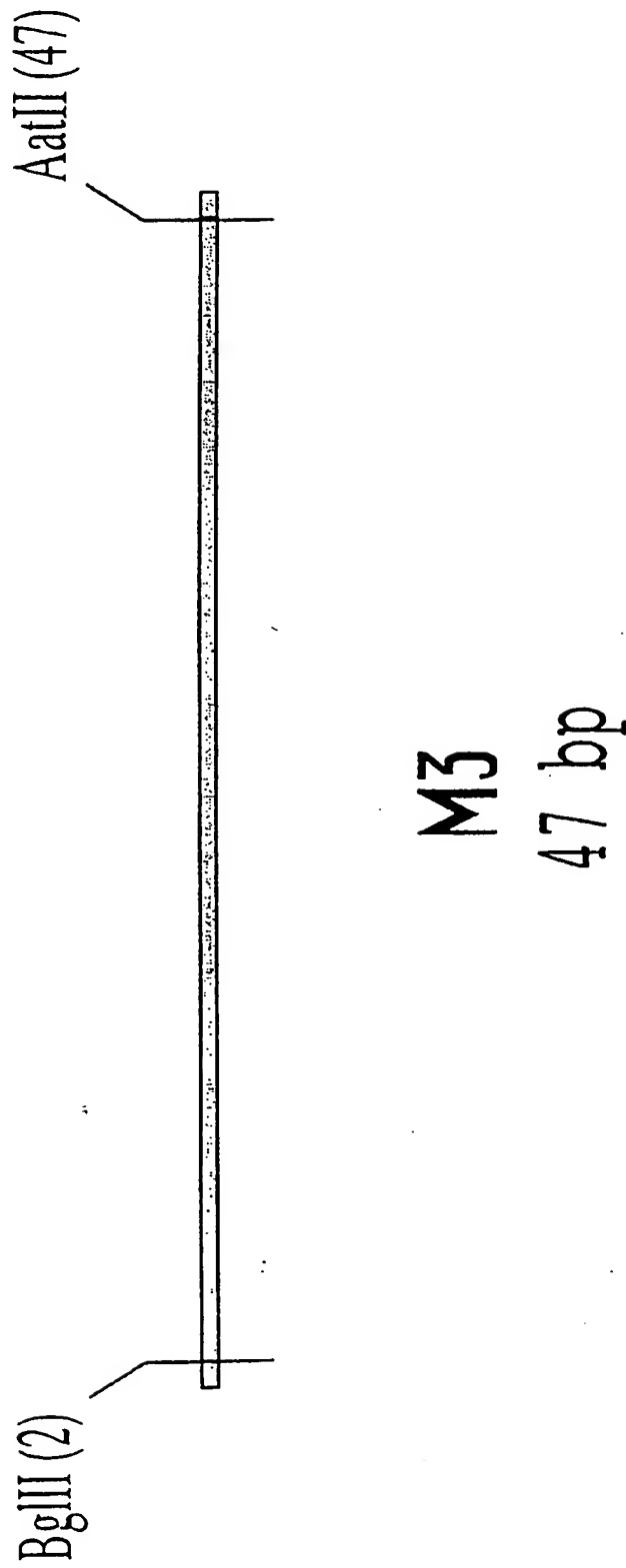


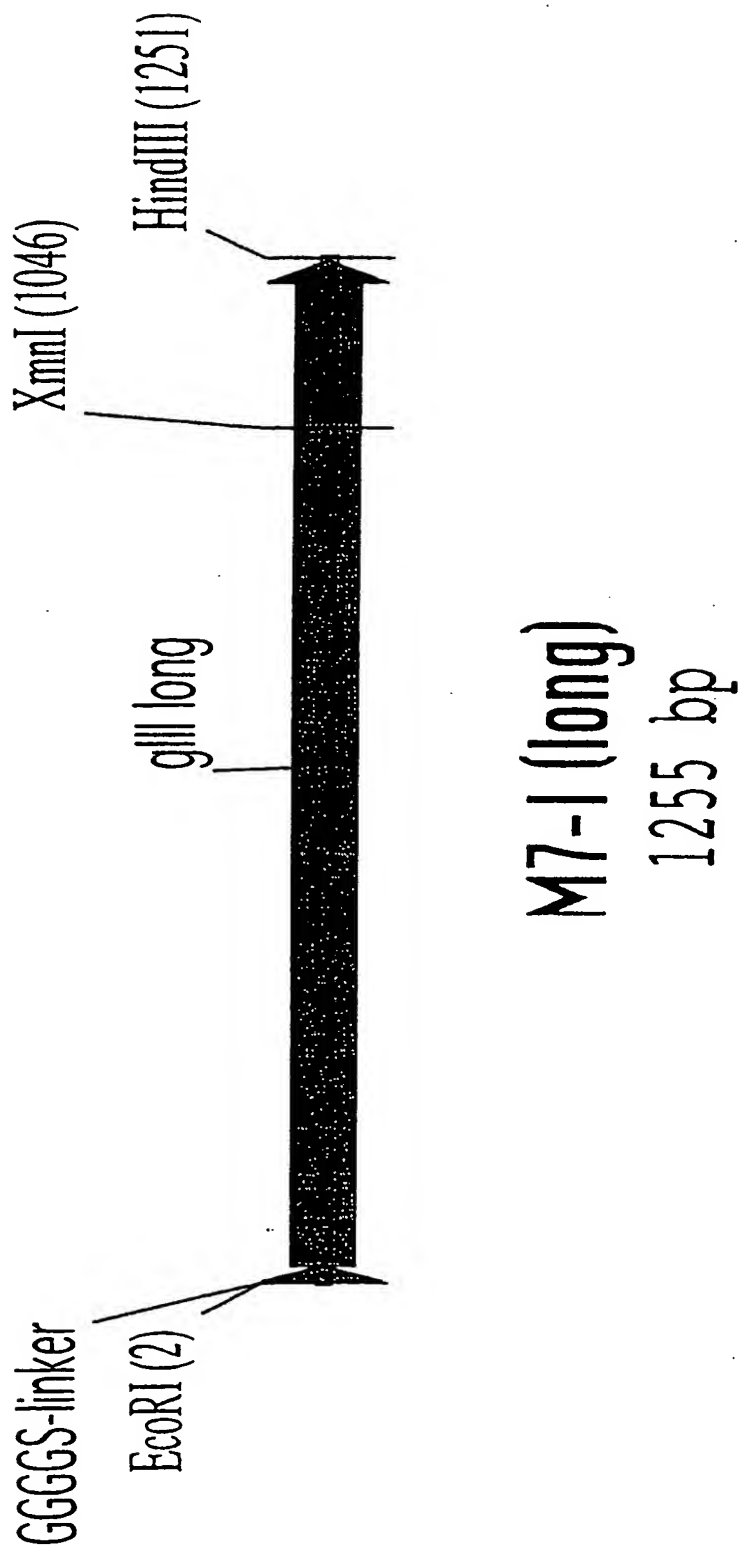
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 3:

	BglII	AatII
	-----	-----
1	AGATCTCATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TGACGTC	
	TCTAGAGTAT TGAAGCATAT TACATACGAT ATGCTTCAAT ACTGCAG	

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 7-I (long):

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      ECORI
      ~~~~~
1  GAATTCGGTG GTGGTGGATC TCGGTGCGCT GAAACGGTTG AAAGTTGTTT
   CTTAAGCCAC CACCACCTAG ACGCACGCGA CTTTGCCAAC TTTC AACAAA

51  AGCAAAATCC CATA CAGAAA ATTCA TTAC TAACGCTCTGG AAAGACGACA
   TCGTTTTAGG GTATGTC TTT TAAGTAAATG ATTGCAGACC TTTCTGCTGT

101 AAAC TT TAGA TCGTTACGCT AACTATGAGG GCTGCTGTG GAATGCTACA
   TTTGAAATCT AGCAATGCCA TTGATACTCC CGACAGACAC CTTACGATGT

151 GGCGTTGTAG TTTGTACTGG TGACGAAACT CAGTGTTACG GTACATGGGT
   CCGCAACATC AAACATGACC ACTGCTTTGA GTCACAAATGC CATGTACCCA

201 TCCTATTGGG CTTGCTATCC CTGAAAATGA GGTGGTGGC TCTGAGGGTG
   AGGATAACCC GAACGATAGG GACTTTTACT CCCACCACCG AGACTCCCCAC

251 GCGGTTCTGA GGTGGCGGT TCTGAGGGTG GCGGTACTAA ACCTCCTGAG
   CGCCAAGACT CCCACCGCCA AGACTCCCAC CGCCATGATT TGGAGGACTC

301 TACGGTGATA CACCTATTCC GGGCTATACT TATATCAACC CTCTCGACGG
   ATGCCACTAT GTGGATAAGG CCCGATATGA ATATAGTTGG GAGAGCTGCC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

351	CACTTATCCG	CCTGGTACTG	AGCAAACCC	CGCTAATCCT	AATCCTTCTC
	GTGAATAGGC	GGACCATGAC	TCGTTTGGG	GCGATTAGGA	TTAGGAAGAG
401	TTGAGGAGTC	TCAGCCTCTT	AATACTTTCA	TGTTTCAGAA	TAAATAGGTTT
	AACTCCTCAG	AGTCGGAGAA	TTATGAAAGT	ACAAAGTCTT	ATTATCCAAG
451	CGAAATAGGC	AGGGGGCATT	AACTGTTTAT	ACGGGCACTG	TTACTCAAGG
	GCTTTATCCG	TCCCCCGTAA	TTGACAAATA	TGCCCGTGAC	AATGAGTTCC
501	CACTGACCCC	GTTAAACTT	ATTACCAGTA	CACTCCTGTA	TCATCAAAAG
	GTGACTGGGG	CAATTTTGAA	TAATGGTCAT	GTGAGGACAT	AGTAGTTTTC
551	CCATGTATGA	CGCTTACTGG	AACGGTAAAT	TCAGAGACTG	CGCTTTCCAT
	GGTACATACT	GCGAATGACC	TTGCCATTTA	AGTCTCTGAC	GCGAAAGGTA
601	TCTGGCTTTA	ATGAGGATTT	ATTGTTTGT	GAATATCAAG	GCCAATCGTC
	AGACCGAAAT	TACTCCTAAA	TAAACAAACA	CTTATAGTTC	CGGTTAGCAG
651	TGACCTGCCT	CAACCTCCTG	TCAATGCTGG	CGGCGGCTCT	GGTGGTGGTT
	ACTGGACGGA	GTTGGAGGAC	AGTTACGACC	GCCGCCGAGA	CCACCACCAA
701	CTGGTGCGG	CTCTGAGGGT	GGTGGCTCTG	AGGGTGGCGG	TTCTGAGGGT
	GACCACCGCC	GAGACTCCCA	CCACCGAGAC	TCCCACCGCC	AAGACTCCCA

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

751	GGCGGCTCTG	AGGAGGCCGG	TTCCGGTGGT	GGCTCTGGTT	CCGGTGATTT
	CCGCCGAGAC	TCCCTCCGCC	AAGGCCACCA	CCGAGACCAA	GGCCACTAAA
801	TGATTATGAA	AAGATGGCAA	ACGCTAAATA	GGGGGCTATG	ACCGAAAATG
	ACTAATACTT	TTCTACCGTT	TCCGATTATT	CCCCCGATAC	TGGCTTTTAC
851	CCGATGAAAA	CGCGCTACAG	TCTGACGCTA	AAGGCAAACT	TGATTCTGTC
	GGCTACTTTT	CGCGGATGTC	AGACTGCCGAT	TTCCGTTTGA	ACTAAGACAG
901	GCTACTGATT	ACGGTGCTGC	TATCGATGGT	TTCATTTGGTG	ACGTTTCCGG
	CGATGACTAA	TGCCACGACG	ATAGCTACCA	AAGTAACCCAC	TGCAAAGGCC
951	CCTTGCTAAT	GGTAATGGTG	CTACTGGTGA	TTTGTCTGGC	TCTAATTCCC
	GGAACGATTA	CCATTACCAC	GATGACCACT	AAAACGACCG	AGATTAAAGG
				Xmn I	~~~~~
1001	AAATGGCTCA	AGTCGGTGAA	GGTGATAATT	CACCTTTAAT	GAATAATTTC
	TTTACCGAGT	TCAGCCACTT	CCACTATTAA	GTGGAAATTA	CTTATTAAAG
1051	CGTCAATATT	TACCTTCCAT	CCCTCAATCG	GTTGAATGTC	GCCCTTTTGT
	GCAGTTATAA	ATGGAAGGTA	GGAGTTAGC	CAACTTACAG	CGGGAAAACA

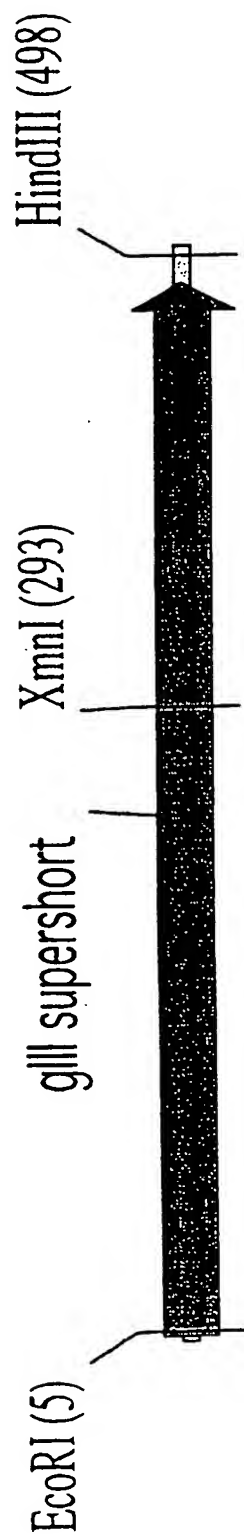
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

1101	CTTTGGCGCT	GGTAAACCCCT	ATGAATTTTC	TATTGATTGT	GACAAAATAA
	GAAACCGCGA	CCATTGGGA	TACTTAAAG	ATAACTAACA	CTGTTTATT
1151	ACTTATTCCG	TGGTGTCCTT	GCGTTTCTTT	TATATGTTGC	CACCTTTATG
	TGAATAAGGC	ACCACAGAAA	CGCAAAGAAA	ATATACAACG	GTGGAAATAC
					HindIII
1201	TATGTATTTT	CTACGTTTGC	TAAACATACTG	CGTAATAAGG	AGTCTTGATA
	ATACATAAAA	GATGCAAACG	ATTGTATGAC	GCATTATTCC	TCAGAACTAT
					HindI

1251	AGCTT				
	TCGAA				

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

**M7-II (ss-TAG)**

502 bp

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 7-II (SS-TAG) :

EcoRI

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1 CGGGAATTCTG GAGGCGGTTC CGGTGGTGGC TCTGGTTCCG GTGATTTGA  
 GCCCTTAAGC CTC CGCCAAG GCCACCACCG AGACCAAGGC CACTAAAACT

51 TTATGAAAAG ATGGCAAACG CTAATAAGGG GGCTATGACC GAAATGCCG  
 AATACTTTTC TACCGTTTGC GATTATTCCC CCGATACTGG CTTTACGGC

101 ATGAAAACGC GCTACAGTCT GACGCTAAAG GCAAACTTGA TTCTGTCGCT  
 TACTTTTGGC CGATGTCAGA CTGCGATTTC CGTTTGAAC TAAACAGCGA

151 ACTGATTACG GTGCTGCTAT CGATGGTTTC ATTGGTGACG TTTCCGGCCT  
 TGACTAATGC CACGACGATA GCTACCAAAG TAACCACTGC AAAGGCCGGA

201 TGCTAATGGT AATGGTGCTA CTGGTGATT TGCTGGCTCT AATCCCAA  
 ACGATTACCA TTACCACGAT GACCACTAAA ACGACCGAGA TTAAGGGTTT

XmnI

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251 TGGCTCAAGT CGGTGACGGT GATAATCAC CTTAATGAA TAATTCCGT
 ACCGAGTTCA GCCACTGCCA CTATTAAGTG GAAATTAATT ATTAAGGCA

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

301	CAATATTAC CTTCCCTCCC TCAATCGGTT GAATGTCGCC CTTTGTCTT	GAAACAGAA
	GTTATAAATG GAAGGAGGG AGTTAGCCAA CTTACAGCGG	
351	TGGCGCTGGT AAACCATATG AATTTCTAT TGATTGTGAC AAAATAAACT	
	ACCGGACCA TTTGGTATAC TTAAGAGATA ACTAACACTG TTTTATTGA	
401	TATCCGTGG TGTCTTTGCG TTTCTTTTAT ATGTTGCCAC CTTATGTAT	
	ATAAGGCACC ACAGAAACGC AAAGAAAATA TACAACGGTG GAAATACATA	
		HindIII

451	GTATTTTCTA CGTTTGCTAA CATACTGCGT AATAAGGAGT CTTGATAAGC	
	CATAAAAGAT GCAAAACGATT GTATGACGCA TTATTCCTCA GAACTATTCTG	
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	~	
501	TT	
	AA	

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 10-II:

BsrGI

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1  GGGGGTGATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA
   CCCCACATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

51 AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTGCC
   TTACGAAGTT ATTATAACTT TTTCCTTCTC ATACTCATAA GTTGTAAGG

101 GTGTCGCCCT TATTCCCTTT TTGCGGCAT TTTGCCCTTCC TGTTTTGTCT
   CACAGCGGGA ATAAGGAAA AAACGCCGTA AAACGGAAGG ACAAACACGA

151 CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAGGATC AGTTGGGTGC
   GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTCCTAG TCAACCCACG

201 GCGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
   CGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT

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## XmnI

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251 GTTTTCGCCC CGAAGAACGT TTCCAATGA TGAGCACTTT TAAAGTTCTG
   CAAAAGCGGG GCTTCTTGCA AAAGGTACT ACTCGTGAAA ATTTCAAGAC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 8:

|   | SphI                                                | HindIII |
|---|-----------------------------------------------------|---------|
|   | ~~~~~                                               | ~~~~~   |
| 1 | GCATGCCATA ACTTCGTATA ATGTACGCTA TACGAAGTTA TAAGCTT |         |
|   | CGTACGGTAT TGAAGCATAT TACATGCGAT ATGCTTCAAT ATTCGAA |         |

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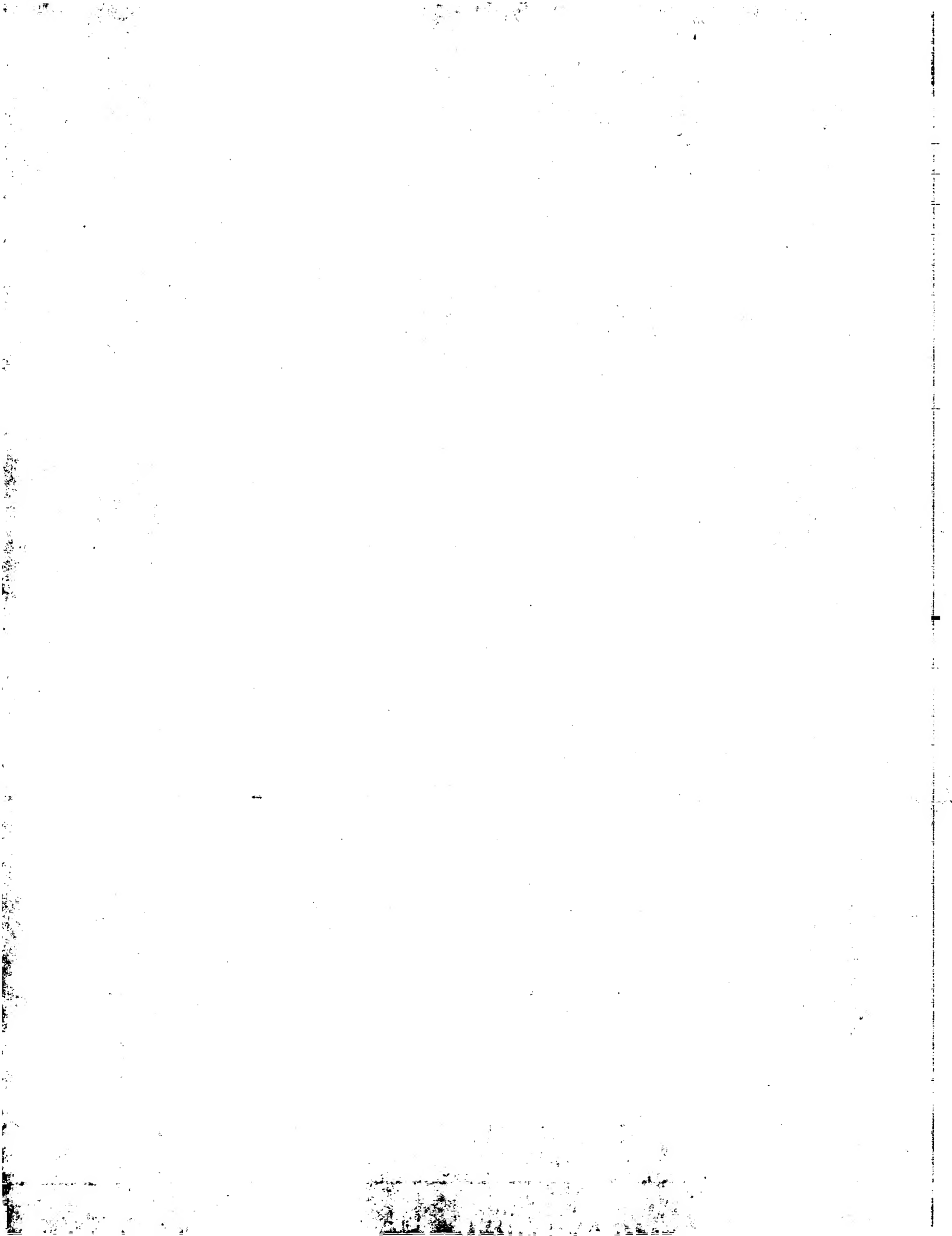




Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

301 ATAGTGGACT CTTGTTCCAA ACTGGACCAA CACTCAACCC TATCTCGGTC  
TATCACCTGA GAACAAGGTT TGACCTTGTT GTGAGTTGGG ATAGAGCCAG

351 TATTCTTTG ATTTATAAGG GATTTTGCCG ATTTGGGCTT ATTGGTTAA  
ATAAGAAAC TAAATATTCC CTAAACCGGC TAAAGCCGGA TAACCAATTT

401 AAATGAGCTG ATTTAACCAA AATTTAACGC GAATTTTAAC AAAATATTAA  
TTTACTCGAC TAAATTGTTT TTAATTGCG CTTAATAATTG TTTTATAATT

BSRGI  
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451 CGTTTACAAT TTCATGTACA
GCAAATGTTA AAGTACATGT

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

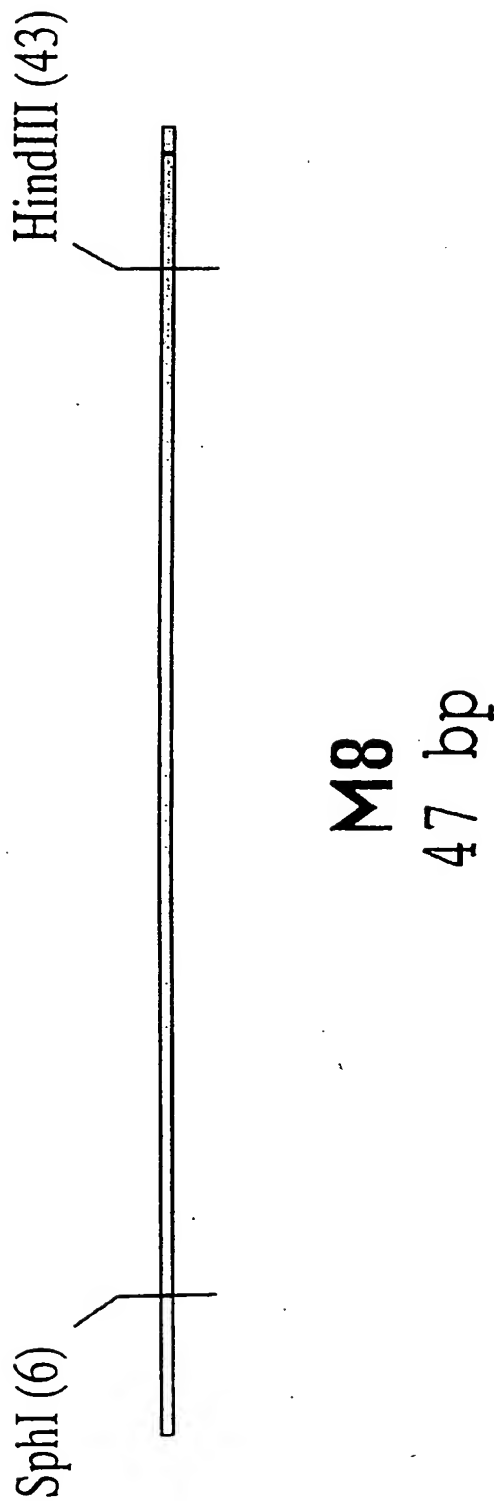


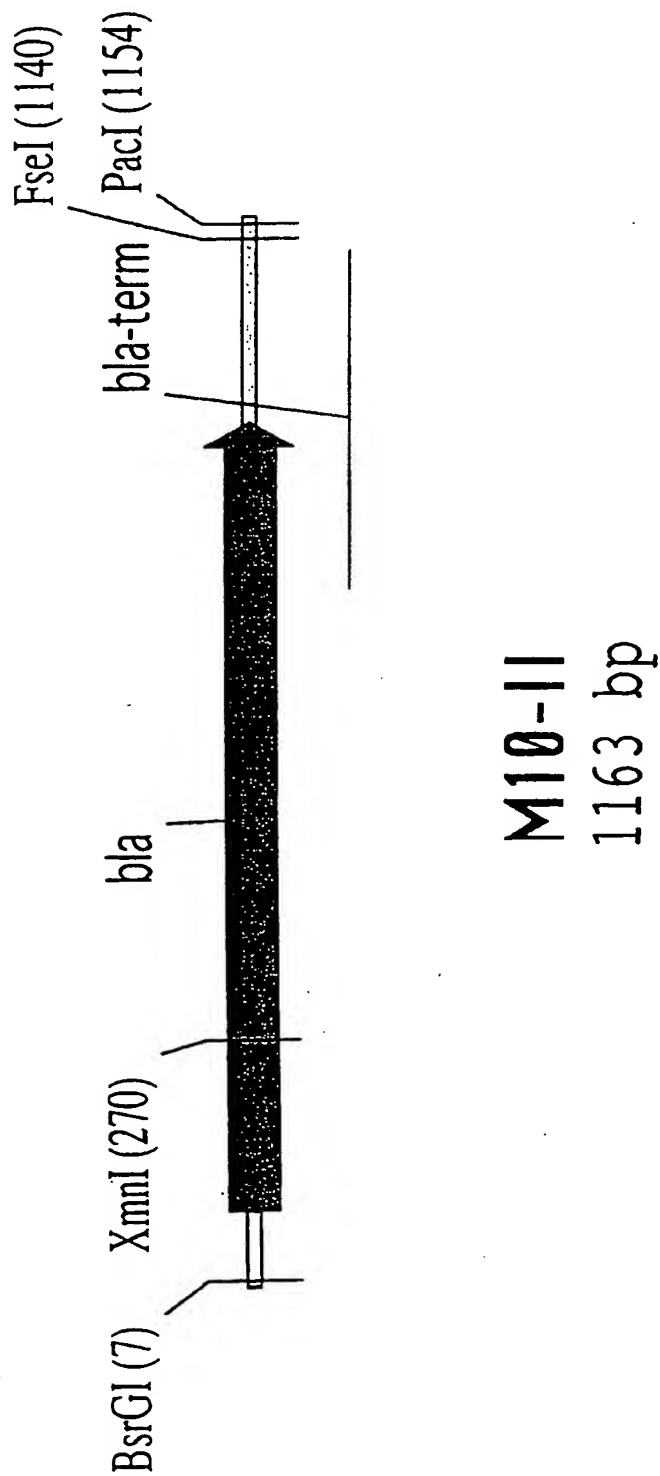
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 8:

	SphI	HindIII
	~~~~~	~~~~~
1	GCATGCCATA ACTTCGTATA ATGTACGCTA TACGAAGTTA TAAGCTT	
	CGTACGGTAT TGAAGCATAT TACATGCGAT ATGCTTCAAT ATTCGAA	

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

## M 10-II:

## BsrGI

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1  GGGGGTGTAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA
   CCCCCACATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

51  AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTGCC
   TTACGAAGTT ATTATAACTT TTTCCCTTCTC ATACTCATAA GTTGTAAGG

101 GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCCTTCC TGTTTTGTCT
   CACAGCGGGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAACACGA

151 CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAGGATC AGTTGGGTGC
   GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTCCTAG TCAACCCACG

201 GCGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
   CGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT

```

XmnI

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251 GTTTTCGCC CGAAGAACGT TTCCAATGA TGAGCACTTT TAAAGTTCTG
   CAAAAGCGGG GCTTCTTGCA AAAGGTACT ACTCGTGAAA ATTTCAAGAC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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301  CTATGTGGCG  CCGTATTATC  CCGTATTGAC  GCCGGGCAAG  AGCAACTCGG
      GATACACCGC  GCCATAAATAG  GGCATAACTG  CGGCCCGTTC  TCGTTGAGCC

351  TCGCCCGCATA  CACTATTCTC  AGAATGACTT  GGTGAGTAC   TCACCAGTCA
      AGCGGCGTAT  GTGATAAGAG  TCTTACTGAA  CCAACTCATG  AGTGGTCAGT

401  CAGAAAAGCA  TCTTACGGAT  GGATGACAG  TAAGAGAAAT  ATGCAGTGCT
      GTCTTTTCGT  AGAATGCCCTA  CCGTACTGTC  ATTCTCTTAA  TACGTCACGA

451  GCCATAACCA  TGAGTGATAA  CACTGCGGCC  AACTTACTTC  TGACAACGAT
      CGGTATTGGT  ACTCACTATT  GTGACGCCGG  TTGAATGAAG  ACTGTTGCTA

501  CGGAGGACCG  AAGGAGCTAA  CCGCTTTTTC  GCACAACATG  GGGATCATG
      GCCTCCTGGC  TTCCTCGATT  GCGAAATAAA  CGTGTGTGAC  CCCCTAGTAC

551  TAACTCGCCT  TGATCGTTGG  GAACCGGAGC  TGAATGAAGC  CATACCAAAC
      ATTGAGCGGA  ACTAGCAACC  CTTGGCCTCG  ACTTACTTCG  GTATGGTTTG

601  GACGAGCGTG  ACACCACGAT  GCCTGTAGCA  ATGGCAACAA  CGTTGCGCAA
      CTGCTCGCAC  TGTGGTGCTA  CGGACATCGT  TACCGTTGTT  GCAACGCGTT

651  ACTATTAACT  GGCGAACTAC  TTACTCTAGC  TTCCCGGCAA  CAGTTAATAG
      TGATAATTGA  CCGCTTGATG  AATGAGATCG  AAGGGCCGTT  GTC AATTATC

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| | | |
|------|---|---|
| 701 | ACTGGATGGA GCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT | TGACCTACCT CCGCCTATT CAACGTCCTG GTGAAGACGC GAGCCGGGAA |
| 751 | CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC | GGCCGACCGA CCAAATAACG ACTATTTAGA CCTCGGCCAC TCGCACCCAG |
| 801 | TCGCGGTATC ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCCTATCG | AGCGCCATAG TAACGTCGTG ACCCCGGTCT ACCATTCTGGG AGGGCATAGC |
| 851 | TAGTTATCTA CACGACGGGG AGTCAGGCCAA CTATGGATGA ACGAAATAGA | ATCAATAGAT GTGCTGCCCC TCAGTCCGTT GATACCTACT TGCTTTATCT |
| 901 | CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTTGG TAACTGTCAG | GTCTAGCGAC TCTATCCACG GAGTGACTAA TTCGTAACCC ATTGACAGTC |
| 951 | ACCAAGTTTA CTCATATATA CTTTAGATTG ATTTAAACT TCATTTTAA | TGGTTCAAAT GAGTATATAT GAAATCTAAC TAAATTTTGA AGTAAAAATT |
| 1001 | TTTAAAAGGA TCTAGGTGAA GATCCTTTT GATAATCTCA TGACCAAAT | AAATTTTCCT AGATCCACTT CTAGGAAAAA CTATTAGAGT ACTGGTTTAA |
| 1051 | CCCTTAACGT GAGTTTTCGT TCCACTGAGC GTCAGACCCC GTAGAAAAGA | GGGAATTGCA CTCAAAAGCA AGTGACTCG CAGTCTGGGG CATCTTTTCT |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| | | FseI | PacI | | |
|------|------------|------------|-----------|------------|------------|
| 1101 | TCAAAGGATC | TTCTTGAGAT | CCTTTTGAT | AATGGCCGGC | CCCCCCCCTT |
| | AGTTCCCTAG | AAGAACTCTA | GGAAAACTA | TTACCGGCCG | GGGGGGGAA |
| | | PacI | | | |
| | | ~~~~~ | | | |
| 1151 | AATTAAGGG | GGG | | | |
| | TTAATTCCCC | CCC | | | |

Figure 3Sa: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

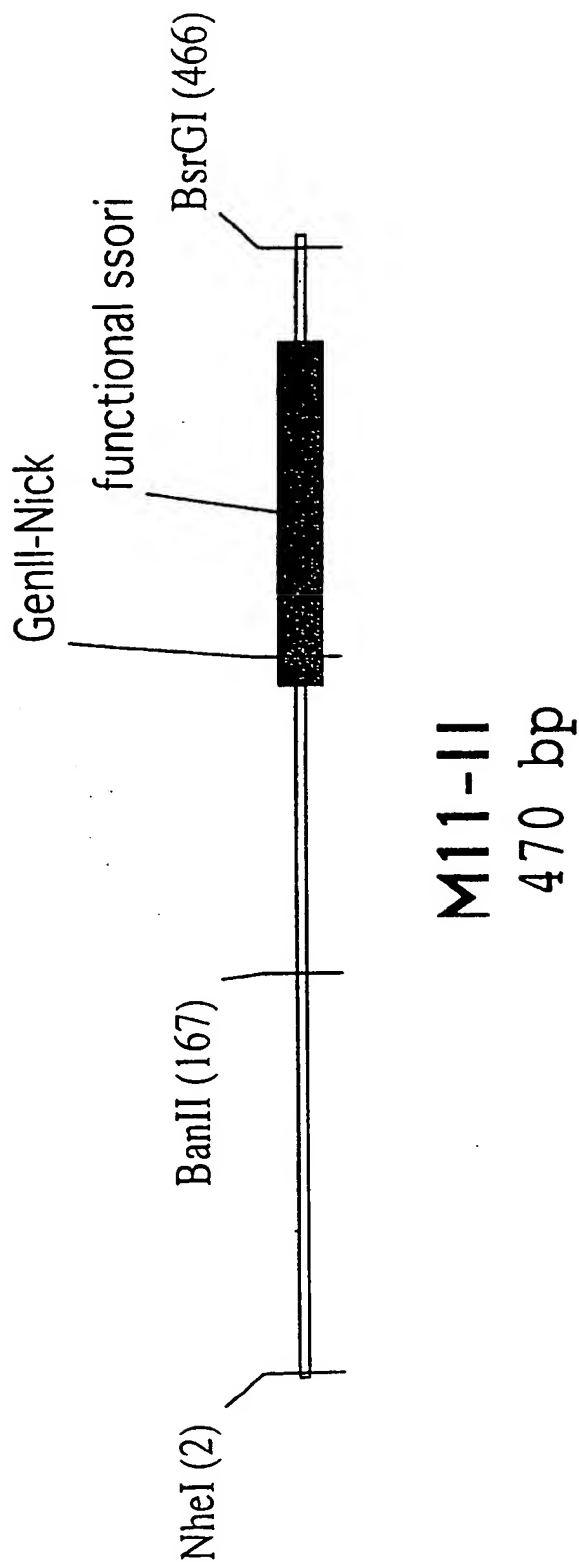


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M11-II:

NheI

1 GCTAGCACGC GCCCTGTAGC GCGGCATTAA GCGCGGCGGG TGTGGTGGTT
CGATCGTGCG CCGGACATCG CCGCGTAATT CCGCGCGCCC ACACCAACCAA

51 ACGCGCAGCG TGACCGCTAC ACTTGCCAGC GCCTAGCGC CCGCTCCTTT
TGCGCGTCGC ACTGGCGATG TGAACGGTCG CCGGATCGCG GCGGAGGAAA

101 CGCTTTCTTC CCTTCCTTTC TCGCCACGTT CGCCGGCTTT CCCCGTCAAG
GCGAAAGAAG GGAAGGAAAG AGCGGTGCAA CCGGCCGAAA GGGCAGTTC

BanII

151 CTCTAAATCG GGGCTCCCTT TTAGGGTTCC GATTAGTGC TTACGGCAC
GAGATTAGC CCGCGAGGGA AATCCCAAGG CTAAATCAGG AAATGCCGTG

201 CTCGACCCCA AAAAATTGA TTAGGGTGAT GGTCTCGTA GTGGGCCATC
GAGCTGGGGT TTTTGAACCT AATCCCACTA CCAAGAGCAT CACCCGGTAG

251 GCCCTGATAG ACGGTTTTTC GCCCTTTGAC GTTGAGTCC ACGTTCTTTA
CGGGACTATC TGCCAAAAAG CCGGAAACTG CAACCTCAGG TGCAAGAAAT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

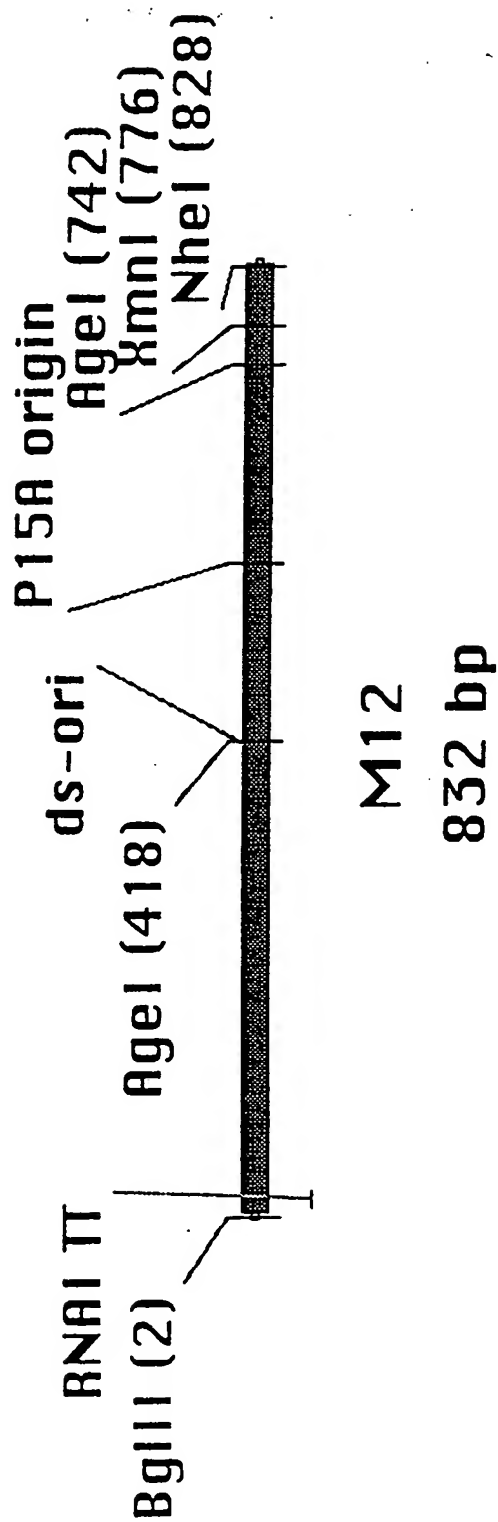


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 12: BglII
 ~~~~~  
 1 AGATCTAATA AGATGATCTT CTTGAGATCG TTTTGGTCTG CGCGTAATCT  
 TCTAGATTAT TCTACTAGAA GAACTCTAGC AAAACGAGAC GCGCATTAGA  
 51 CTTGCTCTGA AAACGAAAA ACCGCTTGC AGGCGGTTT TTCGTAGGTT  
 GACGAGACT TTTGCTTTT TGGCGAACG TCCCGCCAAA AAGCATCCAA  
 101 CTCGAGCTA CCAACTCTT GAACCGAGGT AACTGGCTTG GAGAGCGCA  
 GAGACTCGAT GGTGAGAAA CTGGCTCCA TTGACCGAAC CTCCTCGCGT  
 151 GTCACATAAA CTTGTCCTT CAGTTAGCC TTAACCGCG CATGACTTCA  
 CAGTGATTTT GAACAGGAAA GTCAAATCG AATTGGCCGC GTACTGAACT  
 201 AGACTAACTC CTCATAATCA ATTACCAGTG GCTGCTGCCA CACCACGAAA  
 TCTGATTGAG GAGATTAGT TAAATGGTCAC CGACGACGGT CTATTCCGCG  
 251 TGCATGTCTT TCCGGGTTGG ACTCAAGACG ATAGTTACCG GATAAGGCG  
 ACGTACAGAA AGGCCCAACC TGAGTTCTGC TACAGTCCAG CTTGGAGCGA  
 301 AGCGGTCGGA CTGAACGGG GGTTCGTGCA ATGTCAGGTC GAACCTCGCT  
 TCGCCAGCCT GACTTGCCCC CCAAGCACGT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

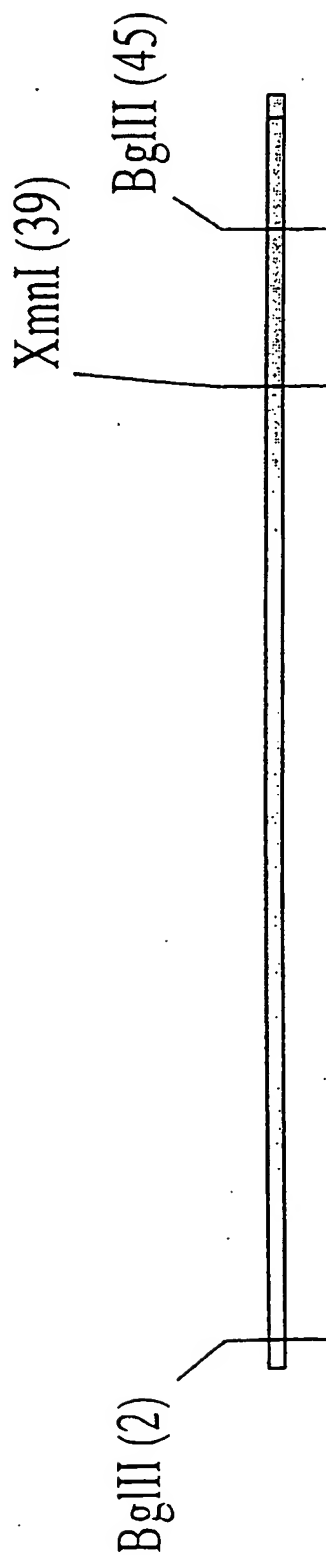
351	ACTGCCCTACC	CGGAACCTGAG	TGTCAGGCGT	GGAATGAGAC	AAACGCGGCC
	TGACGGATGG	GCCTTGACTC	ACAGTCCGCA	CCTTACTCTG	TTTGCGCCCG
AgeI					
~~~~~					
401	ATAACAGCGG	AATGACACCG	GTAACCCGAA	AGGCAGGAAC	AGGAGAGCGC
	TATTGTGCGC	TTACTGTGGC	CATTGGCTT	TCCGTCCCTG	TCCTCTCGCG
451	AGGAGGGAGC	CGCCAGGGGG	AAACGCCCTGG	TATCTTTATA	GTCCCTGTCCG
	TCCTCCCTCG	GCGGTCCCCC	TTTGCGGACC	ATAGAAATAT	CAGGACAGCC
501	GTTTCGCCAC	CACGTATTG	AGCGTCAGAT	TTCGTGATGC	TTGTCAGGGG
	CAAAGCGGTG	GTGACTAAAC	TCGCAGTCTA	AAGCACTACG	AACAGTCCCC
551	GGCGGAGCCT	ATGGAAAAAC	GGCTTTGCCG	CGGCCCTCTC	ACTTCCCCTGT
	CCGCCCTCGA	TACCTTTTGG	CCGAAACGGC	GCCGGGAGAG	TGAAGGGACA
601	TAAGTATCTT	CCTGGCATCT	TCCAGGAAAT	CTCCGCCCCCG	TTCGTAAGCC
	ATTCATAGAA	GGACCGTAGA	AGGTCCTTTA	GAGGCGGGGC	AAGCATTCGG
651	ATTTCGCTC	GCCGCAGTCG	AACGACCGAG	CGTAGCGAGT	CAGTGAGCGA
	TAAAGGCGAG	CGGCGTCAGC	TTGCTGGCTC	GCATCGCTCA	GTCACTCGCT

	Age I	~~~~~
701	GGAAGCGGAA TATATCCTGT ATCACATATT CTGCTGACGC ACCGGTGCAG	
	CCTTCGCCTT ATATAGGACA TAGTGATATA GACGACTGCG TGGCCACGTC	

751 CCTTTTCTT CCTGCCACAT GAAGCACTC ACTGACACCC TCATCAGTGC
GGAAAAAGA GGACGGTGTA CTTCGTGAAG TGACTGTGGG AGTAGTCACG

801 CAACATAGTA AGCCAGTATA CACTCCGCTA GC
GTTGTATCAT TCGGTCATAT GTGAGGCGAT CG

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



M13
49 bp

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 13:

	BglII	XmnI	BglII
	~~~~~	~~~~~	~~~~~
1	AGATCTCATA	ACTTCGTATA	ATGTATGCTA
	TCTAGAGTAT	TGAAGCATAT	TACATACGAT
			ATGCTTCAAT
			AAGTCTAGA



Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

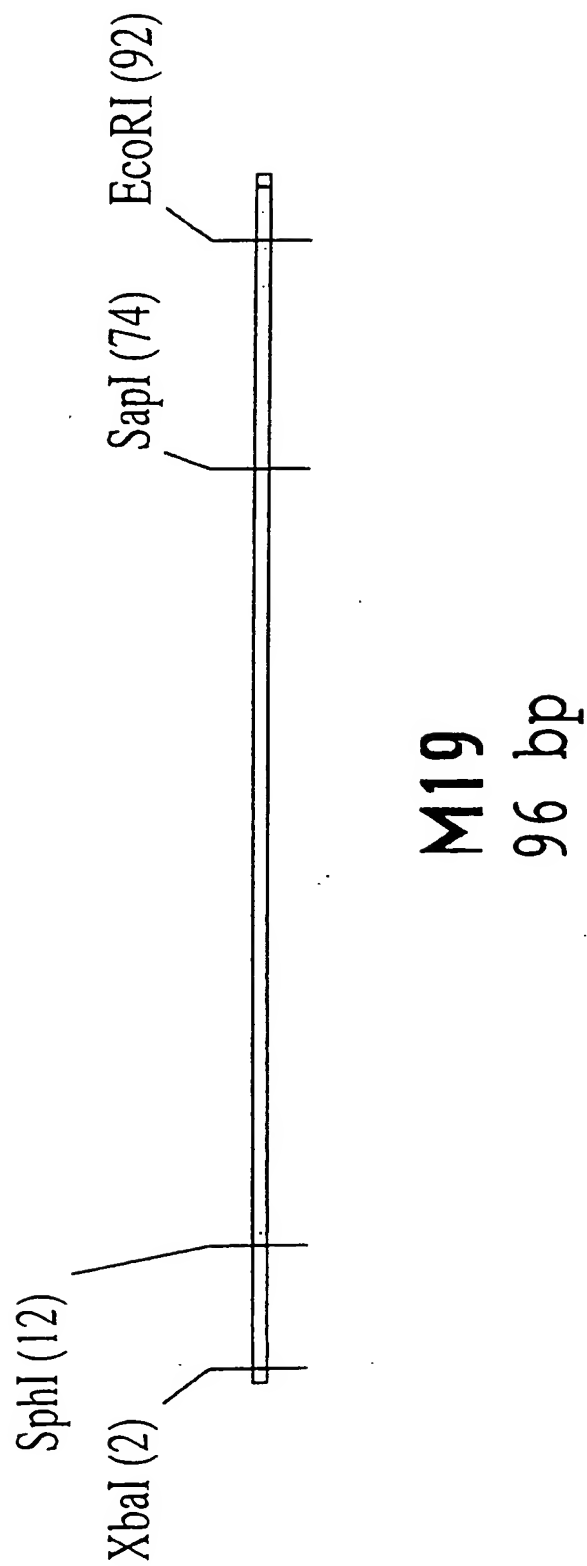


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 19:

XbaI SphI

~~~~~

1 TCTAGAGCAT GCGTAGGAGA AAATAAAATG AAACAAAGCA CTATTGCACT
 AGATCTCGTA CGCATCCTCT TTTATTTTAC TTTGTTTCGT GATAACGTGA

SapI

~~~~~

EcoRI

~~~~~

51 GGCACCTCTTA CCGTTGCTCT TCACCCCTGT TACCAAAGCC GAATTC
 CCGTGAGAAT GGCAACGAGA AGTGGGGACA ATGGTTTCGG CTTAAG

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

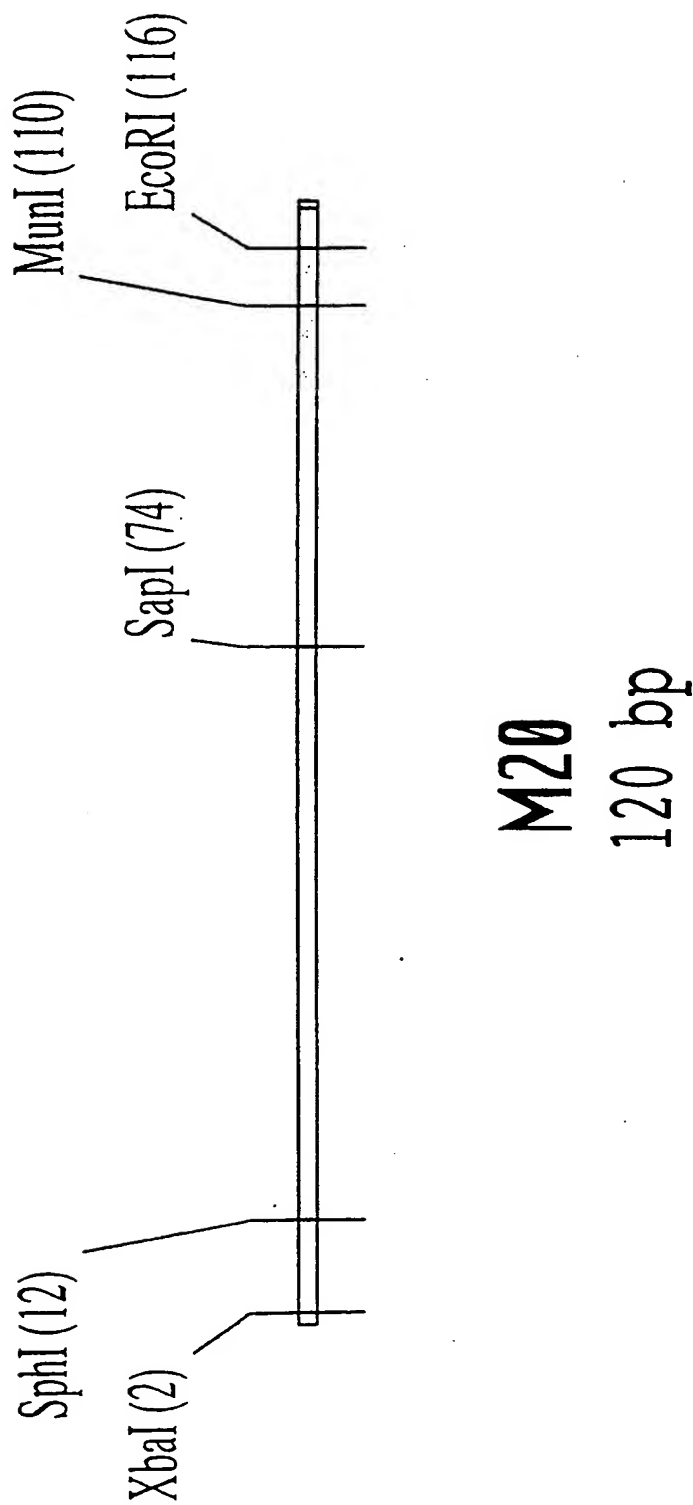


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 20:

| | XbaI | SphI | |
|-----|-------------|------------|----------------------------------|
| | ----- | ----- | |
| 1 | TCTAGAGCAT | CGGTAGGAGA | AAATAAAATG AAACAAGCA CTATTGCACT |
| | AGATCTCGTA | CGCATCCTCT | TTTATTTTAC TTTGTTTCGT GATAACGTGA |
| | | | |
| | | SapI | |
| | | ----- | |
| 51 | GGCACTCTTA | CCGTTGCTCT | TCACCCCTGT TACCAAGCC GACTACAAAG |
| | CCGTGAGAAAT | GGCAACGAGA | AGTGGGGACA ATGGTTTCGG CTGATGTTTC |
| | | | |
| | MunI | EcoRI | |
| | ----- | ----- | |
| 101 | ATGAAGTGCA | ATTGGAATTC | |
| | TACTTCACGT | TAACCTTAAG | |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

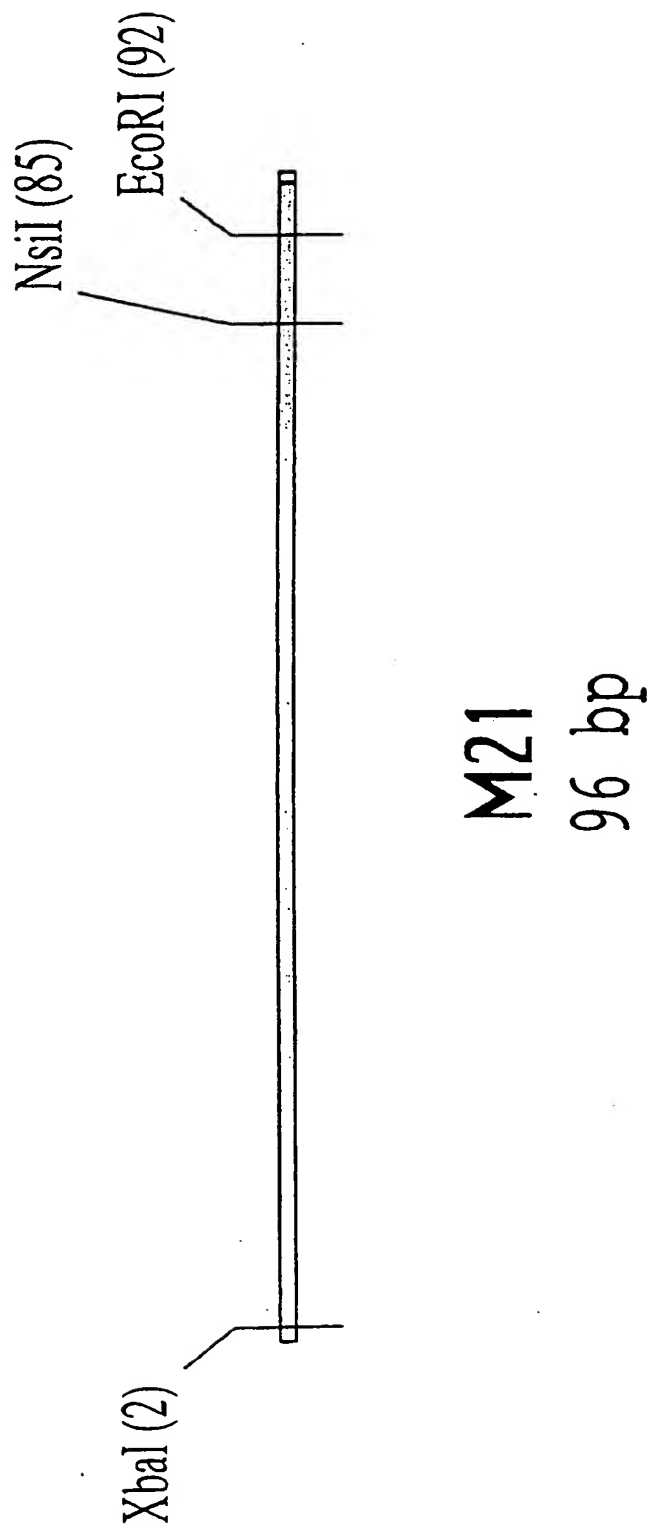


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 21:

XbaI

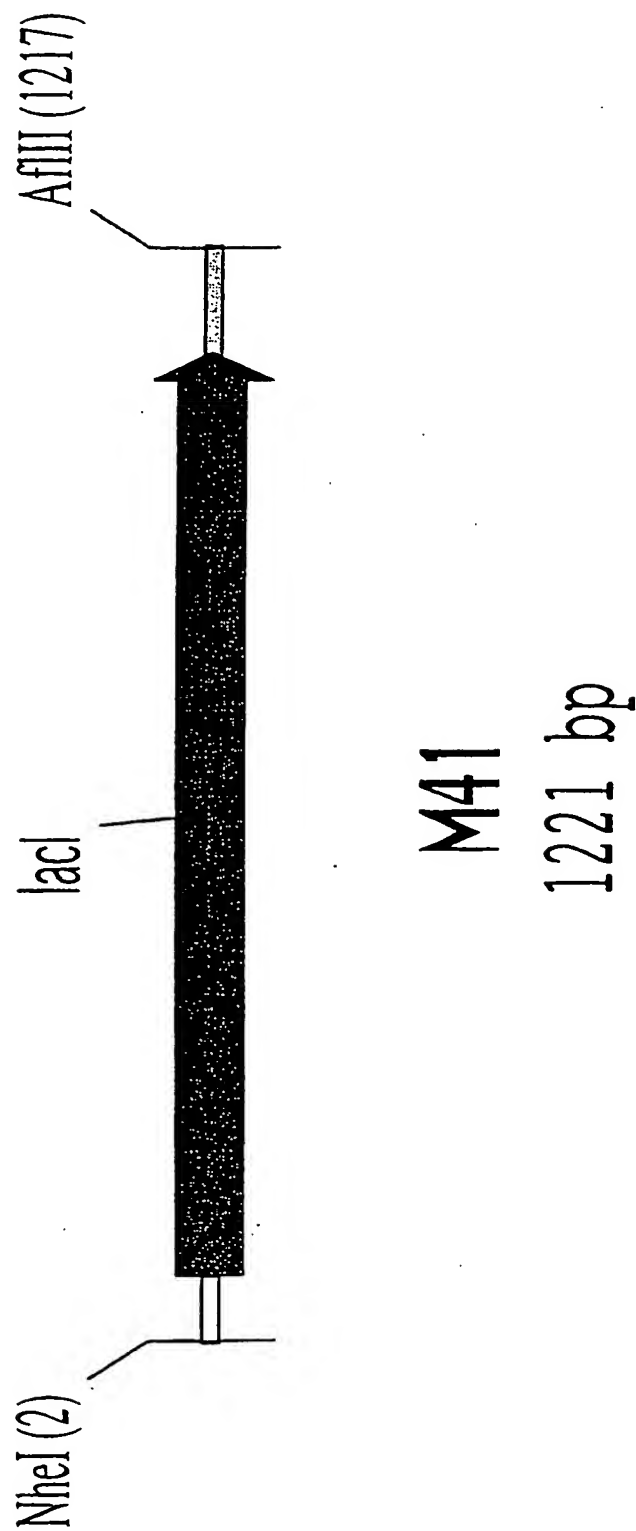
1 TCTAGAGGTT GAGGTGATTT TATGAAAAG AATATCGCAT TTCTTCTTGC
 AGATCTCCAA CTCCACTAAA ATACTTTTC TTATAGCGTA AAGAAGAACG

NsiI EcoRI

51 ATCTATGTC GTTTTCTA TTGCTACAA TGCATACGCT GAATTC
 TAGATACAAG CAAAAAAGAT AACGATGTTT ACGTATGCCA CTTAAG

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 41:

NheI

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1	GCTAGCATCG	AATGGCGCAA	AACCTTTTCGC	GGTATGGCAT	GATAGCGCCC
	CGATCGTAGC	TTACCGCGTT	TTGGAAAGCG	CCATACCGTA	CTATCGCGGG
51	GGAAGAGAGT	CAATTCAGGG	TGGTGAATGT	GAAACCAGTA	ACGTTATACG
	CCTTCTCTCA	GTTAAGTCCC	ACCACTTACA	CTTTGGTCAT	TGCAATATGC
101	ATGTCGCAGA	GTATGCCGGT	GTCTCTTATC	AGACCGTTTC	CCGCGTGGTG
	TACAGCGTCT	CATACGGCCA	CAGAGAATAG	TCTGGCAAAG	GGCGACCCAC
151	AACCAGGCCA	GCCACGTTTC	TGCGAAAACG	CGGGAATAAG	TGGAAGCGGC
	TTGGTCCGGT	CGGTGCAAAG	ACGCTTTTGC	GCCCTTTTTC	ACCTTCGCCC
201	GATGGCGGAG	CTGAATTACA	TTCCCTAACCG	CGTGGCACAA	CAACTGGCGG
	CTACCGCCCTC	GACTTAATGT	AAGGATTGGC	GCACCGTGTT	GTTGACCGCC
251	GCAAACAGTC	GTTGCTGATT	GGCGTTGCCA	CCTCCAGTCT	GGCCCTGCAC
	CGTTTGTGTCAG	CAACGACTAA	CCGCAACGGT	GGAGGTCAGA	CCGGGACGTG
301	GCGCCGTCGC	AAATTGTCCG	GGCGATTAAA	TCTCGCGCCG	ATCAACTGGG
	CGCGGCAGCG	TTTAACAGCG	CCGCTAATTT	AGAGCGCGGC	TAGTTGACCC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

351	TGCCAGCGTG	GTCGTGTCGA	TGGTAGAACG	AAGCGGCGTC	GAAGCCTGTA
	ACGGTCGCAC	CAGCACAGCT	ACCATCTTGC	TTCGCCGCAG	CTTCGGACAT
401	AAGCGGCGGT	GCACAACTCT	CTCGCGCAAC	GTGTCAGTGG	GCTGATTATT
	TTCGCCGCCA	CGTGTTAGAA	GAGCGCGTTG	CACAGTCACC	CGACTAATAA
451	AACTATCCGC	TGGATGACCA	GGATGCTATT	GCTGTGGAAG	CTGCCCTGCAC
	TTGATAGGCG	ACCTACTGGT	CCTACGATAA	CGACACCTTC	GACGGACGTG
501	TAATGTTCCG	GCGTTATTTC	TTGATGTCTC	TGACCAGACA	CCCATCAACA
	ATTACAAGGC	CGCAATAAAG	AACTACAGAG	ACTGGTCTGT	GGTAGTTGT
551	GTATTATTTT	CTCCCATGAG	GACGGTACGC	GACTGGGCGT	GGAGCATCTG
	CATAATAAAA	GAGGGTACTC	CTGCCATGCG	CTGACCCGCA	CCTCGTAGAC
601	GTCGCATTGG	GCCACCAGCA	AATCGCGCTG	TTAGCTGGCC	CATTAAGTTC
	CAGCGTAACC	CGGTGGTCGT	TTAGCGCGAC	AATCGACCGG	GTAATTCAAG
651	TGTCTCGGCG	CGTCTGCCGT	TGGCTGGCTG	GCATAAATAT	CTCACTCGCA
	ACAGAGCCGC	GCAGACGCAG	ACCGACCGAC	CGTATTTATA	GAGTGAGCGT
701	ATCAAATTCA	GCCGATAGCG	GAACGGGAAG	GCGACTGGAG	TGCCATGTCC
	TAGTTTAAGT	CGGCTATCGC	CTTGCCCTTC	CGCTGACCTC	ACGGTACAGG

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

751	GGTTTCAAC	AAACCATGCA	AATGCTGAAT	GAGGGCATCG	TTCCCACCTGC
	CCAAAAGTTG	TTTGGTACGT	TTACGACTTA	CTCCCCTAGC	AAGGGTGACG
801	GATGCTGGTT	GCCAAACGATC	AGATGGCGCT	GGGCGCAATG	CGTGCCATTA
	CTACGACCAA	CGTTGCTAG	TCTACCGCGA	CCCGCGTTAC	GCACGGTAAT
851	CCGAGTCCGG	GCTGCGCGTT	GGTGCGGACA	TCTCGGTAGT	GGGATACGAC
	GGCTCAGGCC	CGACGCGCAA	CCACGCCCTGT	AGAGCCATCA	CCCTATGCTG
901	GATACCGAGG	ACAGCTCATG	TTATATCCCG	CCGCTGACCA	CCATCAAACA
	CTATGGCTCC	TGTCGAGTAC	AATATAGGGC	GGCGACTGGT	GGTAGTTTGT
951	GGATTTTCGC	CTGCTGGGGC	AAACCAGCGT	GGACCGCTTG	CTGCAACTCT
	CCTAAAAGCG	GACGACCCCG	TTTGCTCGCA	CCTGGCGAAC	GACGTTGAGA
1001	CTCAGGGCCA	GGCGGTGAAG	GGCAATCAGC	TGTTGCCCGT	CTCACTGGTG
	GAGTCCCGGT	CCGCCACTTC	CCGTTAGTCG	ACAACGGGCA	GAGTGACCAC
1051	AAAAGAAAAA	CCACCCTGGC	TCCCAATACG	CAAACCGCCT	CTCCCCGCGC
	TTTTCTTTTT	GGTGGGACCG	AGGTTATATG	GTTTGGCGGA	GAGGGGCGCG
1101	GTTGGCCGAT	TCACTGATGC	AGCTGGCACG	ACAGGTTTCC	CGACTGGAAA
	CAACCGGCTA	AGTGACTACG	TCGACCGTGC	TGTCCAAAGG	GCTGACCTTT

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

1151 GCGGGCAGTG AGGCTACCCG ATAAAAGCGG CTTCCCTGACA GGAGGCCCGTT  
CGCCCGTCAC TCCGATGGGC TATTTTCGCC GAAGGACTGT CCTCCGGCAA

AflII

~~~~~

1201 TTGTTTGTGCA GCCCACTTAA G
AACAAAACGT CGGGTGAATT C

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

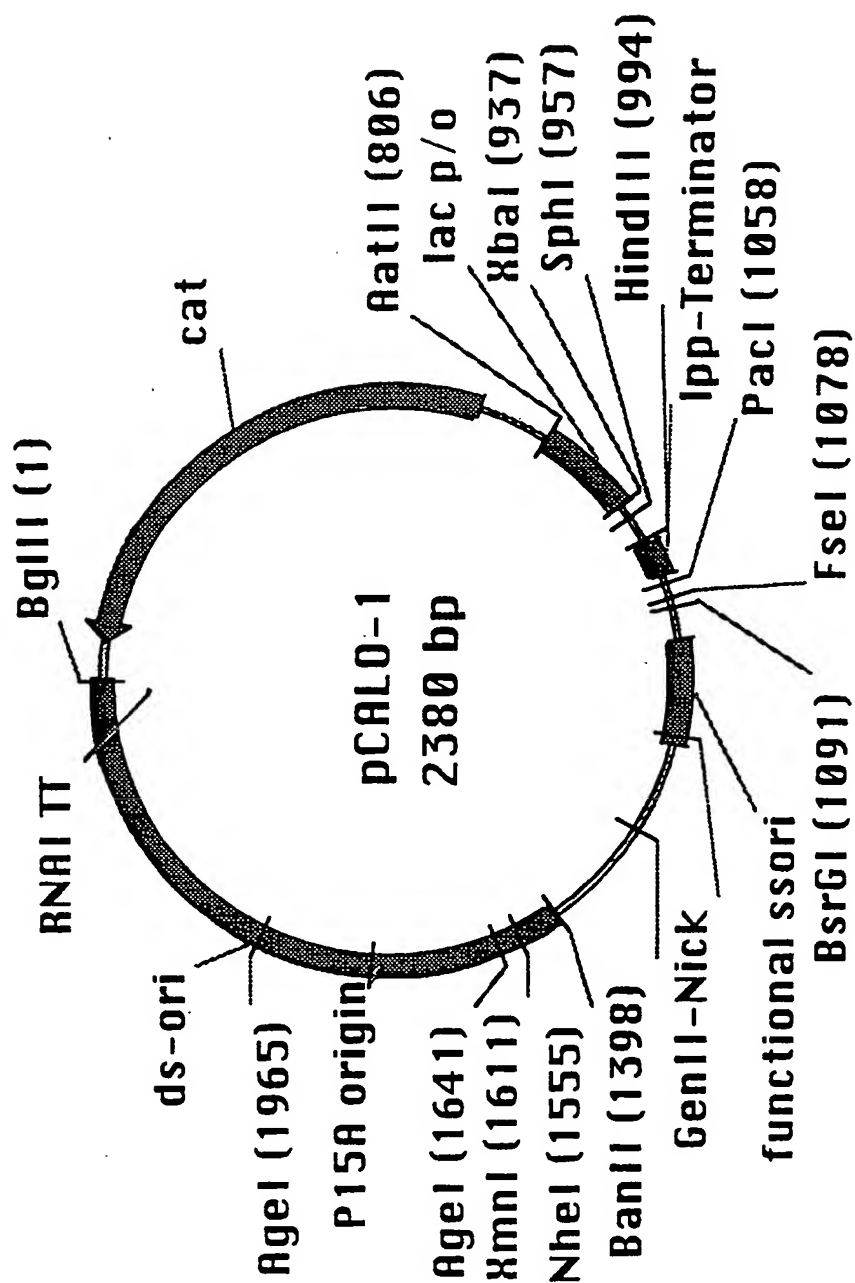


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCAL0-1:
 BglII
 ~~~~~  
 1 GATCTAGCAC CAGCGGTTTA AGGGCACCAA TAACTGCCCTT AAAAAAATTA  
 CTAGATCGTG GTCCGCAAAAT TCCCGTGGTT ATTGACGGAA TTTTTTTAAAT  
 51 CGCCCCGCC TGCCTACTCAT CGCAGTACTG TTGTAATTCA TTAAGCATTC  
 GCGGGCGGG ACGGTGAGTA GCGTCATGAC AACATTAACT AATTCCGTAAG  
 101 TGCCGACATG GAAGCCATCA CAAACGGCAT GATGAACCTG AATCGCCAGC  
 ACGGCTGTAC CTTCGGTAGT GTTTGCCGTA CTAATTGGAC TTAGCGGTCC  
 151 GGCATCAGCA CCTTGTGCGC TTGCGTATAA TATTTGCCCA TAGTGAAAAC  
 CCGTAGTCGT GGAACAGCGG AACGCATATT ATAAACGGGT ATCACTTTTG  
 201 GGGGGCGAAG AAGTTGTCCA TATTGGCTAC GTTTAAATCA AAACCTGGTGA  
 CCCCCGCTTC TTCAACACAGGT ATAAACCGATG CAAATTTAGT TTTGACCACT  
 251 AACTCACCCA GGGATTGGCT GAGACGAAA ACATATTCTC AATAAACCCCT  
 TTGAGTGGGT CCTAACCGA CTCTGCTTTT TGATAAGAG TTATTTGGGA  
 301 TTAGGGAAAT AGGCCAGGTT TTCACCGTAA CACGCCACAT CTTGCCGAATA  
 AATCCCTTTA TCCGGTCCAA AAGTGGCATT GTGCGGTGTA GAACGCTTAT

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

351	TATGTGTAGA ATAACATCT	AACTGCCGGA TTGACGGCCT	AATCGTCGTG TTAGCAGCAC	GTATTCATC CATAAGTGAG	CAGAGCGATG GTCTCGCTAC
401	AAAACGTTTC TTTTTGCAAAG	AGTTTGCTCA TCAAACGAGT	TGGAACAACGG ACCTTTTGCC	TGTAACAAGG ACATTGTTCC	GTGAACACTA CACTTGTGAT
451	TCCCATATCA AGGTATAGT	CCAGCTCACC GGTCGAGTGG	GTCTTTCATT CAGAAAGTAA	GCCATACGGA CGGTATGCCCT	ACTCCGGGTG TGAGGCCCCAC
501	AGCATTCATC TCGTAAGTAG	AGCGGGGCAA TCCGCCCGTT	GAATGTGAAT CTTACACTTA	AAAGGCCCGGA TTTCCGGCCT	TAAAACTTGT ATTTTGAACA
551	GCTTATTTT CGAATAAAAA	CTTTACGGTC GAAATGCCAG	TTTAAAAAGG AAATTTTTC	CCGTAATATC GGCATATAG	CAGCTGAACG GTCGACTTGC
601	GTCTGGTTAT CAGACCAATA	AGGTACATTG TCCATGTAAC	AGCAACTGAC TCGTTGACTG	TGAAATGCCCT ACTTTACGGA	CAAAATGTTC GTTTACAAAG
651	TTTACGATGC AAATGCTACG	CATTGGGATA GTAACCCCTAT	TATCAACGGT ATAGTTGCCA	GGTATATCCA CCATATAGGT	GTGATTTTTT CACTAAAAAA
701	TCTCCATTTT AGAGGTAAAA	AGCTTCCTTA TCGAAGGAAT	GCTCCTGAAA CGAGGACTTT	ATCTCGATAA TAGAGCTATT	CTCAAAAAAT GAGTTTTTTA

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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751  ACGCCCGGTA  GTGATCTTAT  TTCATTATGG  TGAAAGTTGG  AACCTCACCC
      TCGGGGCCAT  CACTAGAATA  AAGTAATACC  ACTTCAACC  TTGGAGTGGG

      AatII
      ~~~~~
801 GACGTCTAAT GTGAGTTAGC TCACTCATTA GGCACCCAG GCTTTACACT
 CTGCAGATTA CACTCAATCG AGTGAGTAAT CCGTGGGTC CGAAATGTGA

851 TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT
 AATACGAAGG CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA

 XbaI
      ~~~~~
901  CACACAGGAA  ACAGCTATGA  CCATGATTAC  GAATTTCTAG  ACCCCCCCCC
      GTGTGTCCTT  TGTCGATACT  GGTAATAATG  CTTAAAGATC  TGGGGGGGGG

      SphI
      ~~~~~
 HindIII
      ~~~~~
951  CGCATGCCAT  AACTTCGTAT  AATGTACGCT  ATACGAAGTT  ATAAGCTTGA
      GCGTACGGTA  TTGAAGCATA  TTACATGCCA  TATGCTTCAA  TATTCGAAC

1001  CCTGTGAAGT  GAAAATGGC  GCAGATTGTG  CGACATTTT  TTTGTCTGCC
      GGACACTTCA  CTTTTTACCG  CGTCTAACAC  GCTGTAAAAA  AAACAGACGG

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

	PacI	FseI	BsrGI
	~~~~~	~~~~~	~~~~~
1051	GTTTAATTAA AGGGGGGGG GGGCCGGCCT GGGGGGGGT GTACATGAAA		
	CAAAATTAATT TCCCCCCCCC CCGGCCGGA CCCCCCCCA CATGACTTT		
1101	TTGTAAACGT TAATATTTTG TTAAATTCG CGTTAAATTT TTGTAAATC		
	AACATTTGCA ATTATAAAC AATTTAAGC GCAATTTAA AACAAATTAG		
1151	AGCTCATTTT TTAACCAATA GGCCGAAATC GGCAAAATCC CTTATAAATC		
	TCGAGTAAA AATTGGTTAT CCGCCTTAG CCGTTTAGG GAATATTAG		
1201	AAAAGAATAG ACCGAGATAG GGTGAGTGT TGTTCCAGTT TGGAACAAGA		
	TTTCTCTATC TGGCTCTATC CCAACTCACA ACAAGGTCAA ACCTTGTTCT		
1251	GTCCACTATT AAAGAACGTG GACTCCAACG TCAAAGGCGG AAAAACCGTC		
	CAGGTGATAA TTCTTGCAC CTGAGGTTGC AGTTTCCCGC TTTTTCGCAG		
1301	TATCAGGGCG ATGGCCCACT ACGAGAACCA TCACCCTAAT CAAGTTTTT		
	ATAGTCCCCG TACCGGGTGA TGCTCTTGGT AGTGGGATTA GTTCAAAAAA		
1351	GGGTCGAGG TGCCGTAAAG CACTAAATCG GAACCCATAA GGGAGCCCCC		
	CCCCAGCTCC ACGGCATTTC GTGATTTAGC CTTGGGATT CCCTCGGGG		
			BanII
			~~~~~

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

1401	GATTAGAGC TTGACGGGGA AAGCCGGCGA ACGTGGCGAG AAAGGAAGGG CTAAATCTCG AACTGCCCTT TTCGGCCGCT TGCACCGCTC TTTCTTCCC
1451	AAGAAAGCGA AAGGAGCGGG CGCTAGGGCG CTGGCAAGTG TAGCGGTCAC TTCCTTTCGCT TTCCTCGCCC GCGATCCCGC GACCGTTCAC ATCGCCAGTG
1501	GCTGCGCGTA ACCACCACAC CCGCCGCGCT TAATGCGCCG CTACAGGGCG CGACGCGCAT TGGTGGGTGTG GCGGCGCGGA ATTACGCGGC GATGTCCCGC
	NheI ~~~~~
1551	CGTGCTAGCG GAGTGATATAC TGGCTTACTA TGTGGCACT GATGAGGGTG GCACGATCGC CTCACATATG ACCGAATGAT ACAACCGTGA CTACTCCCAC
	XmnI ~~~~~
1601	TCAGTGAAGT GCTTCATGTG GCAGGAGAAA AAAGGCTGCA CCGGTGCGTC AGTCACTTCA CGAAGTACAC CGTCCTCTTT TTTCCGACGT GGCCACGCAG
1651	AGCAGAATAT GTGATACAGG ATATATTCCG CTTCCCTCGCT CACTGACTCG TCGTCTTATA CACTATGTCC TATATAAGGC GAAGGAGCGA GTGACTGAGC
1701	CTACGCTCGG TCGTTCGACT GCGGCGAGCG GAAATGGCTT ACGAACGGGG

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued).

	GATGCGAGCC	AGCAAGCTGA	CGCCGCTCGC	CTTTACCGAA	TGCTTGCCCC
1751	CGGAGATTTC	CTGGAAGATG	CCAGGAAGAT	ACTTAACAGG	GAAGTGAGAG
	GCCCTCTAAG	GACCTTCTAC	GGTCCCTTCTA	TGAATTGTCC	CTTCACTCTC
1801	GGCCGCGGCA	AAGCCGTTT	TCCATAGGCT	CCGCCCCCCT	GACAAGCATC
	CCGGCGCCGT	TTCGGCAAAA	AGTATCCGA	GGCGGGGGA	CTGTTCGTAG
1851	ACGAAATCTG	ACGCTCAAAT	CAGTGGTGGC	GAAACCCGAC	AGGACTATAA
	TGCTTTAGAC	TGCGAGTTTA	GTCACCAACG	CTTTGGGCTG	TCCCTGATATT
1901	AGATACCAGG	CGTTTCCCCC	TGGCGGCTCC	CTCCTGCGCT	CTCCTGTTC
	TCTATGGTCC	GCAAAGGGGG	ACCGCCGAGG	GAGGACGCCA	GAGGACAAGG
AgeI					
~~~~~					
1951	TGCCCTTTCGG	TTTACCGGTG	TCATTCCGCT	GTTATGGCCG	CGTTTGTCTC
	ACGGAAAGCC	AAATGGCCAC	AGTAAGGCCA	CAATACCGGC	GCAAACAGAG
2001	ATTCCACGCC	TGACACTCAG	TTCCGGGGTAG	GCAGTTCGCT	CCAAGCTGGA
	TAAGGTGCCG	ACTGTGAGTC	AAGGCCCATC	CGTCAAGCGA	GGTTCGACCT
2051	CTGTATGCAC	GAACCCCCCG	TTCAGTCCGA	CCGCTGCGCC	TTATCCGGTA
	GACATACGTG	CTTGGGGGGC	AAGTCAGGCT	GGCGACGCGG	AATAGGCCAT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

2101	ACTATCGTCT	TGAGTCCAAC	CCGAAAGAC	ATGCAAAAGC	ACCACTGGCA
	TGATAGCAGA	ACTCAGGTG	GGCCTTCTG	TACGTTTTCG	TGGTGACCGT
2151	GCAGCCACTG	GTAATTGATT	TAGAGGAGTT	AGTCTTGAAG	TCATGCGCCG
	CGTCGGTGAC	CATTAACTAA	ATCTCCTCAA	TCAGAACTTC	AGTACGCGGC
2201	GTTAAGGCTA	AACTGAAAGG	ACAAGTTTAA	GTGACTGCCG	TCCTCCAAGC
	CAATTCCGAT	TTGACTTTCC	TGTTCAAAAT	CACTGACGCG	AGGAGGTTCCG
2251	CAGTTACCTC	GGTTCAAAGA	GTTGGTAGCT	CAGAGAACCCT	ACGAAAACC
	GTCAATGGAG	CCAAGTTTCT	CAACCATCGA	GTCTCTTGGA	TGCTTTTGG
2301	GCCCTGCAAG	GCGGTTTTTT	CGTTTTCAGA	GCAAGAGATT	ACGCGCAGAC
	CGGGACGTTT	CGCCAAAAAA	GCAAAAGTCT	CGTCTCTTAA	TGCGCGTCTG
BglII					
2351	CAAAACGATC	TCAAGAAGAT	CATCTTATTA		
	GTTTGTGCTAG	AGTTCTTCTA	GTAGAATAAT		

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

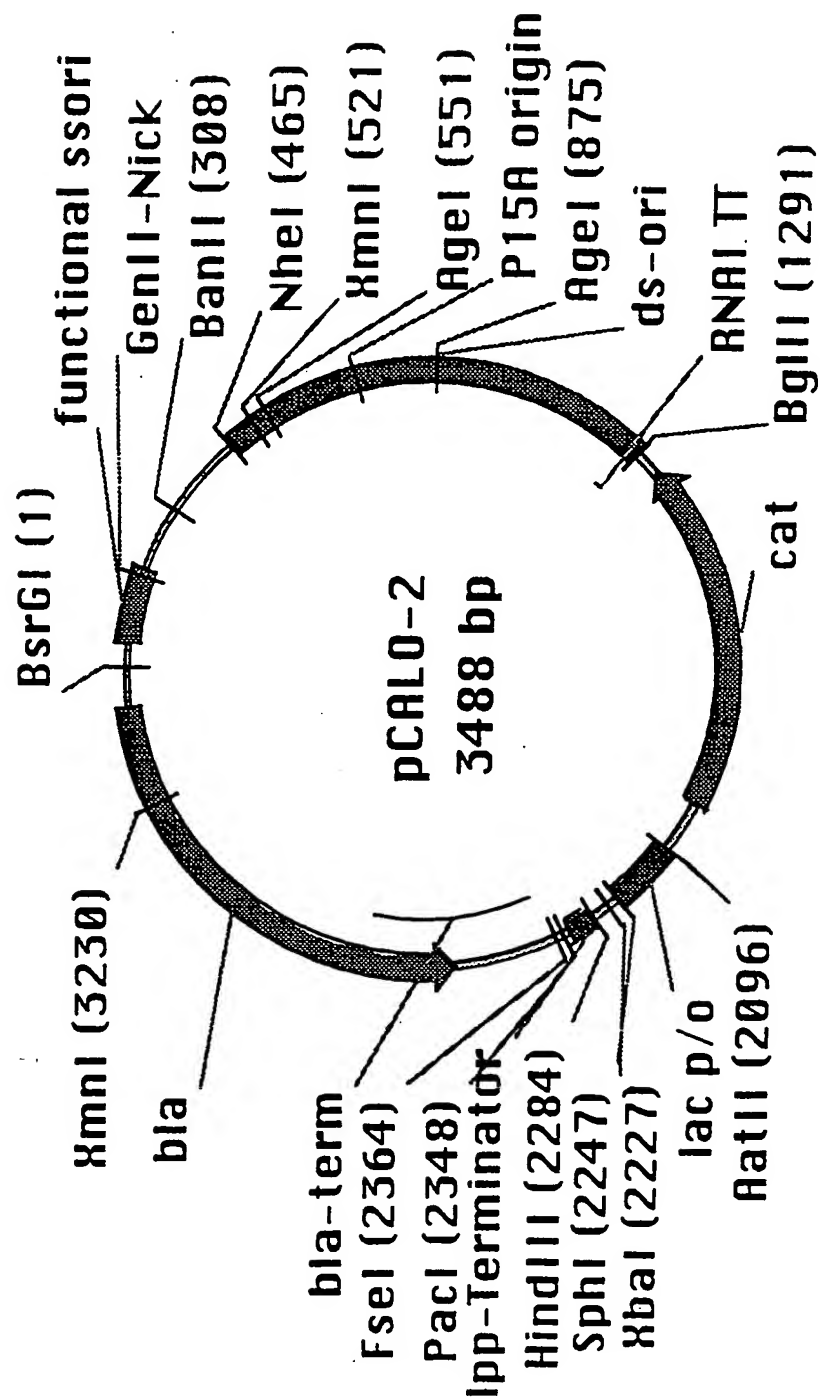


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCALO-2:

BsrGI

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|     |             |             |             |             |             |
|-----|-------------|-------------|-------------|-------------|-------------|
| 1   | GTACATGAAA  | TTGTAAACGT  | TAATATTTTG  | TTAAAATTCC  | CGTTAAATTT  |
|     | CATGACTTTT  | AACATTTGCA  | ATTATAAAAC  | AATTTTAAGC  | GCAATTTAAA  |
| 51  | TTGTTAAATC  | AGCTCATTTT  | TTAACCAATA  | GGCCGAAATC  | GGCAAAATCC  |
|     | AACAATTAG   | TCGAGTAAAA  | AATTGGTTAT  | CCGGCTTTAG  | CCGTTTTAGG  |
| 101 | CTTATAAATC  | AAAAGAAATAG | ACCGAGATAG  | GGTTGAGTGT  | TGTTCCAGTT  |
|     | GAATATTTAG  | TTTTCCTTATC | TGGCTCTATC  | CCAAC TCACA | ACAAGGTCAA  |
| 151 | TGGAACAAGA  | GTCCACTATT  | AAAGAACGTG  | GACTCCAACG  | TCAAAGGGCG  |
|     | ACCTTGTTCT  | CAGGTGATAA  | TTTCTTTGCAC | CTGAGGTTGC  | AGTTTCCCGC  |
| 201 | AAAACCCGTC  | TATCAGGGCG  | ATGGCCCACT  | ACGAGAACCA  | TCACCCCTAAT |
|     | TTTTTTGGCAG | ATAGTCCCGC  | TACCGGGTGA  | TGCTCTTGGT  | AGTGGGATTA  |
| 251 | CAAGTTTTT   | GGGGTCGAGG  | TGCCGTAAAG  | CACTAAATCG  | GAACCCCTAAA |
|     | GTTCAAAAAA  | CCCCAGCTCC  | ACGGCATTTT  | GTGATTTAGC  | CTTGGGATTT  |
|     | BanII       |             |             |             |             |
|     | ~~~~~       |             |             |             |             |
| 301 | GGGAGCCCCC  | GATTTAGAGC  | TTGACGGGGA  | AAGCCGGCGA  | ACGTGGCGAG  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

CCCTCGGGG  CTAAATCTCG  AACTGCCCTT  TTCGGCCGCT  TGCACCGCTC

351  AAAGGAAGG  AAGAAAGCGA  AAGAGCGGG  CGTAGGGCG  CTGGCAAGTG
      TTTCCCTTCC  TTCTTTTCGCT  TTCCCTCGCC  GCGATCCCCG  GACCGTTCAC

401  TAGCGGTCAC  GCTGCGCGTA  ACCACCACAC  CCGCCGCGCT  TAATGCGCCG
      ATCGCCAGTG  CGACGCGCAT  TGGTGGTGTG  GCGGCGCGGA  ATTACGCGGC

                                NheI
                                ~~~~~
451 CTACAGGGCG CGTGCTAGCG GAGTGATAC TGGCTTACTA TGTGCGCACT
 GATGTCCCGC GCACGATCGC CTCACATATG ACCGAATGAT ACAACCGTGA

 XmnI
                                ~~~~~
501  GATGAGGGTG  TCAGTGAAGT  GCTTCATGTG  GCAGGAGAAA  AAAGGCTGCA
      CTACTCCCGC  AGTCACTTCA  CGAAGTACAC  CGTCCCTCTT  TTTCCGACGT

AgeI
~~~~~
551 CCGGTGCGTC AGCAGAATAT GTGATACAGG ATATATTCCG CTTCCCTCGCT
 GGCCACGCAG TCGTCTTATA CACTATGTCC TATATAAGGC GAAGGAGCGA

601 CACTGACTCG CTACGCTCGG TCGTTCGACT GCGGCGAGCG GAAATGGCTT

```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |             |            |              |             |            |
|-----|-------------|------------|--------------|-------------|------------|
|     | GTGACTGAGC  | GATGCGAGCC | AGCAAGCTGA   | CGCCGCTCGC  | CTTTACCGAA |
| 651 | ACGAAACGGGG | CGGAGATTTC | CTGGAAGATG   | CCAGGAAGAT  | ACTTAACAGG |
|     | TGCTTGCCCC  | GCCTCTAAAG | GACCTTCTAC   | GGTCCCTTCTA | TGAATTGTCC |
| 701 | GAAGTGAGAG  | GGCCGCGGCA | AAGCCGTTT    | TCCATAGGCT  | CCGCCCCCT  |
|     | CTTCACTCTC  | CCGGCGCCGT | TTCGGCAAAA   | AGGTATCCGA  | GGCGGGGGA  |
| 751 | GACAAGCATC  | ACGAAATCTG | ACGCTCAAAT   | CAGTGGTGGC  | GAAACCCGAC |
|     | CTGTTTCGTAG | TGCTTTAGAC | TGCGAGTTTA   | GTCACCAACCG | CTTTGGGCTG |
| 801 | AGGACTATAA  | AGATACCAGG | CGTTTCCCCC   | TGGCGGCTCC  | CTCCTGCGCT |
|     | TCCTGATATT  | TCTATGGTCC | GCAAAGGGG    | ACCGCCGAGG  | GAGGACGCCA |
|     |             |            | AgeI         |             |            |
|     |             |            | ~~~~~        |             |            |
| 851 | CTCCTGTTCC  | TGCCTTTCGG | TTTACC GG TG | TCATTCCGCT  | GTTATGGCCG |
|     | GAGGACAAGG  | ACGGAAGCC  | AAATGGCCAC   | AGTAAGCGCA  | CAATACCCGC |
| 901 | CGTTTGTC TC | ATTCCACGCC | TGACACTCAG   | TTCCGGGTAG  | GCAGTTCGCT |
|     | GCAAACAGAG  | TAAGGTGCGG | ACTGTGAGTC   | AAGCCCCATC  | CGTCAAGCGA |
| 951 | CCAAGCTGGA  | CTGTATGCAC | GAACCCCCCG   | TTCAGTCCGA  | CCGCTGCGCC |
|     | GGTTCGACCT  | GACATACGTG | CTTGGGGGGC   | AAGTCAGGCT  | GGCGACGCGG |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |            |            |             |             |             |
|-------|------------|------------|-------------|-------------|-------------|
| 1001  | TTATCCGGTA | ACTATCGTCT | TGAGTCCAAC  | CCGGAAGAC   | ATGCAAAAGC  |
|       | AATAGGCCAT | TGATAGCAGA | ACTCAGGTG   | GGCCTTTCTG  | TACGTTTTCG  |
| 1051  | ACCACTGGCA | GCAGCCACTG | GTAATTGATT  | TAGAGGAGTT  | AGTCTTGAAG  |
|       | TGGTGACCGT | CGTCGGTGAC | CATTAACTAA  | ATCTCCTCAA  | TCAGAACTTC  |
| 1101  | TCATGCGCCG | GTTAAGGCTA | AACTGAAAGG  | ACAAGTTTTA  | GTGACTGCCG  |
|       | AGTACGCGGC | CAATTCCGAT | TTGACTTTCC  | TGTTCAAAT   | CACTGACGCG  |
| 1151  | TCCTCCAAGC | CAGTTACCTC | GGTCAAAGA   | GTTGGTAGCT  | CAGAGAACCT  |
|       | AGGAGGTTCC | GTCAATGGAG | CCAAGTTTCT  | CAACCATCGA  | GTCTCTTGGA  |
| 1201  | ACGAAAAACC | GCCCTGCAAG | GCGGTTTTTT  | CGTTTTCAGA  | GCAAGAGATT  |
|       | TGCTTTTGG  | CGGGACGTC  | CGCCAAAAAA  | GCAAAAGTCT  | CGTTCCTCTAA |
| BgIII |            |            |             |             |             |
| 1251  | ACGCGCAGAC | CAAACGATC  | TCAAGAAGAT  | CATCTTATTA  | GATCTAGCAC  |
|       | TGCGCGTCTG | GTTTGTCTAG | AGTTCTTCTA  | GTAGAATAAT  | CTAGATCGTG  |
| 1301  | CAGGCGTTTA | AGGGCACCAA | TAACTGCCCTT | AAAAAAATTA  | CGCCCCGCC   |
|       | GTCCGCAAAT | TCCCGTGGTT | ATTGACGGAA  | TTTTTTTAAAT | GCGGGGCGGG  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |            |             |             |             |
|------|-------------|------------|-------------|-------------|-------------|
| 1351 | TGCCACTCAT  | CGCAGTACTG | TTGTAATTCA  | TTAAGCATTTC | TGCCGACATG  |
|      | ACGGTGAGTA  | GCGTCATGAC | AACATTAAAGT | AATTCGTAAG  | ACGGCTGTAC  |
| 1401 | GAAGCCATCA  | CAAACGGCAT | GATGAACCTG  | AATCGCCAGC  | GGCATCAGCA  |
|      | CTTCGGTAGT  | GTTTGCCGTA | CTACTTGGAC  | TTAGCGGTCC  | CCGTAGTCGT  |
| 1451 | CCTTGTCGCC  | TTGCGTATAA | TATTTGCCCA  | TAGTGAAAC   | GGGGCGAAG   |
|      | GGAACAGCGG  | AACGCATATT | ATAAACGGGT  | ATCACTTTTG  | CCCCCGCTTC  |
| 1501 | AAGTTGTCCA  | TATTGGCTAC | GTTTAAATCA  | AAACTGGTGA  | AACTCACCCA  |
|      | TTCAACACAGT | ATAACCGATG | CAAATTTAGT  | TTTGACCACT  | TTGAGTGGGT  |
| 1551 | GGGATTGGCT  | GAGACGAAA  | ACATATTCTC  | AATAAACCCCT | TTAGGGAAAT  |
|      | CCCTAAACCGA | CTCTGCCTTT | TGTATAAGAG  | TTATTTGGGA  | AATCCCTTTA  |
| 1601 | AGGCCAGGTT  | TTACCCGTAA | CACGCCACAT  | CTTGCGAATA  | TATGTGTAGA  |
|      | TCCGGTCCAA  | AAGTGGCATT | GTGCGGTGTA  | GAACGCTTAT  | ATACACATCT  |
| 1651 | AACTGCCGGA  | AATCGTCGTG | GTATTCACCTC | CAGAGCGATG  | AAAACGTTTC  |
|      | TTGACGGCCT  | TTAGCAGCAC | CATAAGTGAG  | GTCCTCGCTAC | TTTTTGCAAAG |
| 1701 | AGTTTGCTCA  | TGGAAAACGG | TGTAACAAGG  | GTGAACACTA  | TCCCATATCA  |
|      | TCAAACGAGT  | ACCTTTTGCC | ACATTGTTCC  | CACCTGTGAT  | AGGGTATAGT  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |             |             |            |             |            |
|-------|-------------|-------------|------------|-------------|------------|
| 1751  | CCAGCTCACC  | GTCTTTCATT  | GCCATACGGA | ACTCCGGGTG  | AGCATTCATC |
|       | GGTCGAGTGG  | CAGAAAGTAA  | CGGTATGCCT | TGAGGCCCCAC | TCGTAAGTAG |
| 1801  | AGGCGGGCAA  | GAATGTGAAT  | AAAGGCCGGA | TAAAACTTGT  | GCTTATTTT  |
|       | TCCGCCCGTT  | CTTACACTTA  | TTTCCGGCCT | ATTTTGAACA  | CGAATAAAAA |
| 1851  | CTTTACGGTC  | TTTAAAAGG   | CCGTAATATC | CAGCTGAACG  | GTCTGGTTAT |
|       | GAAATGCCAG  | AAATTTTCC   | GGCATTATAG | GTCGACTTGC  | CAGACCAATA |
| 1901  | AGGTACATTG  | AGCAACTGAC  | TGAAATGCCT | CAAAATGTTT  | TTTACGATGC |
|       | TCCATGTAAC  | TCGTTGACTG  | ACTTTACGGA | GTTTACAAG   | AAATGCTACG |
| 1951  | CATTGGGATA  | TATCAACGGT  | GGTATATCCA | GTGATTTTTT  | TCTCCATTTT |
|       | GTAACCCCTAT | ATAGTTGCCA  | CCATATAGGT | CACTAAAAAA  | AGAGGTAAAA |
| 2001  | AGCTTCCTTA  | GCTCCTGAAA  | ATCTCGATAA | CTCAAAAAAT  | ACGCCCGGTA |
|       | TCGAAAGGAAT | CGAGGACTTT  | TAGAGCTATT | GAGTTTTTTA  | TGCGGGCCAT |
| AatII |             |             |            |             |            |
| ~~~~~ |             |             |            |             |            |
| 2051  | GTGATCTTAT  | TTCATTTATGG | TGAAAGTTGG | AACCTCACCC  | GACGTCTAAT |
|       | CACTAGAAATA | AAGTAATACC  | ACTTTCAACC | TTGGAGTGGG  | CTGCAGATTA |
| 2101  | GTGAGTTAGC  | TCACTCATTA  | GGACCCCAG  | GCTTTACACT  | TTATGCTTCC |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            |            |             |            |             |
|------|------------|------------|-------------|------------|-------------|
|      | CACTCAATCG | AGTGAGTAAT | CCGTGGGGTC  | CGAAATGTGA | AATACGAAGG  |
| 2151 | GGCTCGTATG | TTGTGTGGAA | TTGTGAGCGG  | ATAACAATT  | CACACAGGAA  |
|      | CCGAGCATAC | AACACACCTT | AACACTCGCC  | TATTGTTAA  | GTGTGTCCCTT |
|      |            |            | XbaI        |            | SphI        |
|      |            |            | ~~~~~       |            | ~~~~~       |
| 2201 | ACAGCTATGA | CCATGATTAC | GAATTTCCTAG | ACCCCCCCC  | CGCATGCCAT  |
|      | TGTCGATACT | GGTACTAATG | CTTAAAGATC  | TGGGGGGGG  | GCGTACGGTA  |
|      |            |            |             | HindIII    |             |
|      |            |            |             | ~~~~~      |             |
| 2251 | AACTTCGTAT | AATGTACGCT | ATACGAAGTT  | ATAAGCTTGA | CCTGTGAAGT  |
|      | TTGAAGCATA | TTACATGCCA | TATGCTTCAA  | TATTCGAACT | GGACACTTCA  |
|      |            |            |             |            | PacI        |
|      |            |            |             |            | ~~~~~       |
| 2301 | GAAAAATGGC | GCAGATTGTG | CGACATTTT   | TTTGTCTGCC | GTTTAATTAA  |
|      | CTTTTACCG  | CGCTAACAC  | GCTGTAAAAA  | AAACAGACGG | CAAATTAATT  |
|      |            |            |             | FseI       |             |
|      |            |            | ~~~~~       |            |             |
| 2351 | GGGGGGGGGC | CGGCCATTAT | CAAAAAGGAT  | CTCAAGAAGA | TCCTTTGATC  |
|      | CCCCCCCCCG | GCCGGTAATA | GTTTTCCTA   | GAGTCTTCT  | AGGAAACTAG  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |            |            |             |            |
|------|-------------|------------|------------|-------------|------------|
| 2401 | TTTTCTACGG  | GGTCTGACGC | TCAGTGGAAC | GAAAACTCAC  | GTTAAGGGAT |
|      | AAAAGATGCC  | CCAGACTGCG | AGTCACCTTG | CTTTTGAGTG  | CAATTCCCTA |
| 2451 | TTTGGTCATG  | AGATTATCAA | AAAGGATCTT | CACCTAGATC  | CTTTTAAATT |
|      | AAACCAGTAC  | TCTAATAGTT | TTTCCTAGAA | GTGGATCTAG  | GAAAAATTAA |
| 2501 | AAAAATGAAG  | TTTTAAATCA | ATCTAAAGTA | TATATGAGTA  | AACTTGGTCT |
|      | TTTTTTACTTC | AAAATTTAGT | TAGATTTCAT | ATATACTCAT  | TTGAACCAGA |
| 2551 | GACAGTTACC  | CAATGCTTAA | TCAGTGAGGC | ACCTATCTCA  | GCGATCTGTC |
|      | CTGTCAATGG  | GTTACGAATT | AGTCACTCCG | TGGATAGAGT  | CGCTAGACAG |
| 2601 | TATTTCGTTC  | ATCCATAGTT | GCCTGACTCC | CCGTCGTGTA  | GATAACTACG |
|      | ATAAAGCAAG  | TAGGTATCAA | CGGACTGAGG | GGCAGCACAT  | CTATTGATGC |
| 2651 | ATACGGGAGG  | GCTTACCATC | TGGCCCCAGT | GCTGCAATGA  | TACCGCGAGA |
|      | TATGCCCTCC  | CGAATGGTAG | ACCGGGGTCA | CGACGTTACT  | ATGGCGCTCT |
| 2701 | CCCACGCTCA  | CCGGCTCCAG | ATTATCAGC  | AATAAACCAG  | CCAGCCGGAA |
|      | GGTGCGGAGT  | GGCCGAGGTC | TAAATAGTCG | TTATTGGTC   | GGTCGGCCTT |
| 2751 | GGGCCGAGCG  | CAGAAGTGGT | CCTGCAACTT | TATCCGCCCTC | CATCCAGTCT |
|      | CCCGGCTCGC  | GTCTTCACCA | GGACGTTGAA | ATAGCGGGAG  | GTAGGTCAGA |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            |             |              |            |             |
|------|------------|-------------|--------------|------------|-------------|
| 2801 | ATTAACTGTT | GCCGGGAAGC  | TAGAGTAAGT   | AGTTCGCCAG | TTAATAGTTT  |
|      | TAATTGACAA | CGGCCCTTCG  | ATCTCATTCA   | TCAAGCGGTC | AATTATCAAA  |
| 2851 | GCGCAACGTT | GTTGCCATTG  | CTACAGGCAT   | CGTGGTGTC  | CGCTCGTCGT  |
|      | CGCGTTGCAA | CAACGGTAAC  | GATGTCCGTA   | GCACACAGT  | GCGAGCAGCA  |
| 2901 | TTGGTATGGC | TTCAATTCAGC | TCCGGTTCCC   | AACGATCAAG | GCGAGTTACA  |
|      | AACCATACCG | AAGTAAGTCG  | AGGCCAAGGG   | TTGCTAGTTC | CGCTCAATGT  |
| 2951 | TGATCCCCCA | TGTTGTGCAA  | AAAAGCGGTT   | AGTCCCTTCG | GTCCCTCCGAT |
|      | ACTAGGGGGT | ACAACACGTT  | TTTTCGCCAA   | TCGAGGAAGC | CAGGAGGCTA  |
| 3001 | CGTTGTCAGA | AGTAAGTTGG  | CCGCAGTGTT   | ATCACTCATG | GTTATGGCAG  |
|      | GCAACAGTCT | TCATTCAACC  | GCGGTCACAA   | TAGTGAGTAC | CAATACCGTC  |
| 3051 | CACTGCATAA | TTCTCTTACT  | GTCAATGCCAT  | CCGTAAGATG | CTTTTCTGTG  |
|      | GTGACGTATT | AAGAGAATGA  | CAGTACGGTA   | GGCATTCTAC | GAAAAGACAC  |
| 3101 | ACTGGTGAGT | ACTCAACCAA  | GTCAATTCCTGA | GAATAGTGTA | TGCGGCGACC  |
|      | TGACCACTCA | TGAGTTGGTT  | CAGTAAGACT   | CTTATCACAT | ACGCCGCTGG  |
| 3151 | GAGTTGCTCT | TGCCCGGCGT  | CAATACGGGA   | TAATACCGCG | CCACATAGCA  |
|      | CTCAACGAGA | ACGGGCCGCA  | GTTATGCCCT   | ATTATGGCGC | GGTGATTCGT  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| Xmn I |                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------|
| ~~~~~ |                                                                                                                   |
| 3201  | GAAC TTTAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG GCGAAAACTC<br>CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC CGCTTTTGAG |
| 3251  | TCAAGGATCT TACCGCTGTT GAGATCCAGT TCGATGTAAC CCACTCGCGC<br>AGTTCCTAGA ATGGCGACAA CTCTAGGTCA AGCTACATTG GGTGAGCGCG  |
| 3301  | ACCCAACTGA TCCTCAGCAT CTTTACTTT CACCAGCGTT TCTGGGTGAG<br>TGGGTTGACT AGGAGTCGTA GAAATGAAA GTGGTCGCAA AGACCCACTC    |
| 3351  | CAAAAACAGG AAGGCAAAAT GCCGCAAAA AGGGAATAAG GCGACACGG<br>GTTTTTGTCC TTCCGTTTTA CGGCGTTTTT TCCCTTATTC CCGCTGTGCC    |
| 3401  | AAATGTTGAA TACTCATACT CTTCCTTTTT CAATATTATT GAAGCATTTA<br>TTTACAACTT ATGAGTATGA GAAGGAAAAA GTTATAATAA CTCGTAATAAT |
| BsrGI |                                                                                                                   |
| 3451  | TCAGGGTTAT TGTCTCATGA GCGGATACAT ATTTGAAT<br>AGTCCCAATA ACAGAGTACT CGCCTATGTA TAAACTTA                            |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

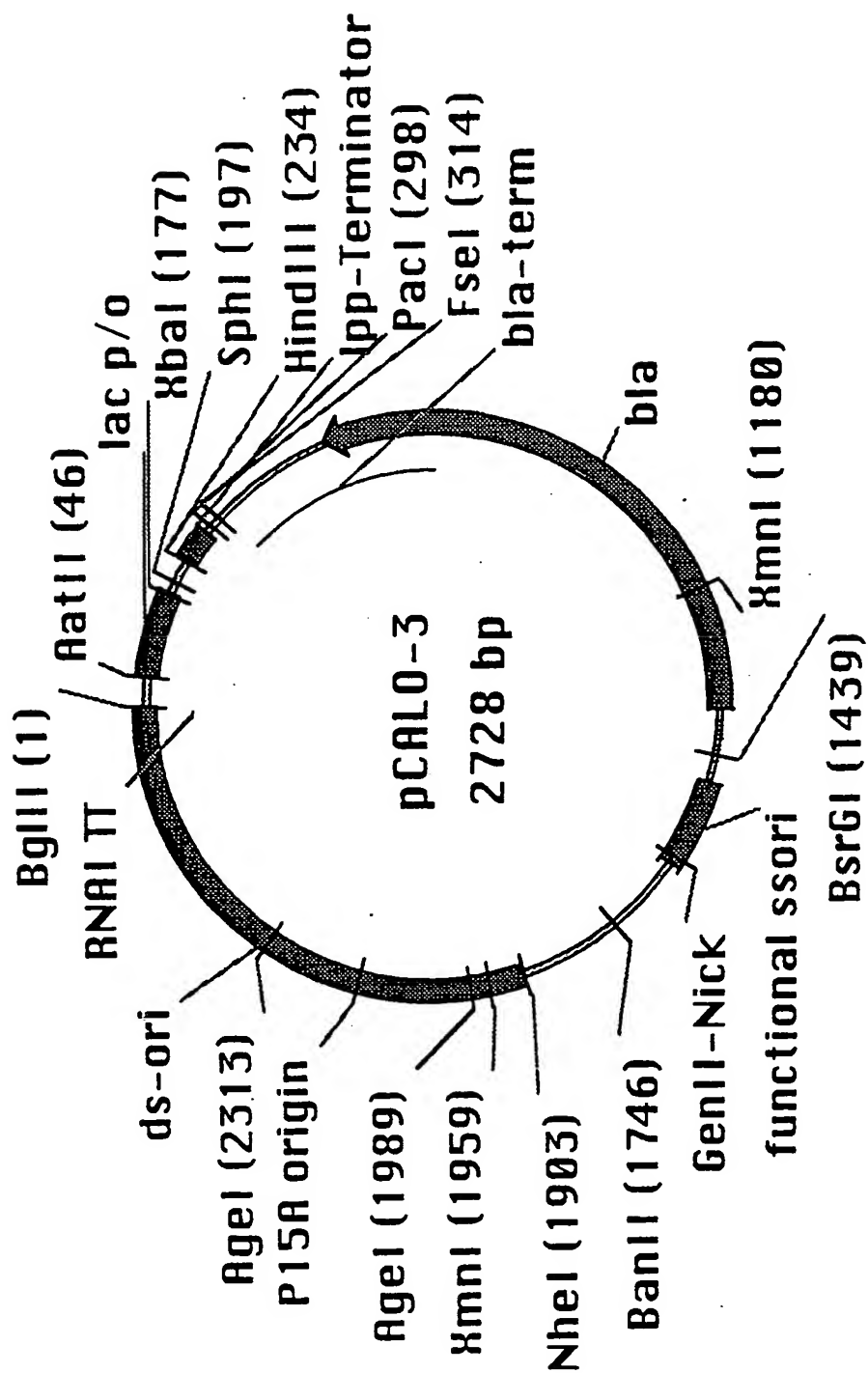


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| pCALO-3:                                                   |             |
|------------------------------------------------------------|-------------|
| BglII                                                      | AatII       |
| ~~~~~                                                      | ~~~~~       |
| 1 GATCTCATAA CTTCGTATAA TGTATGCTAT ACGAAGTTAT GACGTCTAAT   | CTGACAGATTA |
| CTAGAGTATT GAAGCATATT ACATACGATA TGCTTCAATA                |             |
| 51 GTGAGTTAGC TCACTCATTG GGCACCCCGAG GCTTTACACT TTATGCTTCC | AATACGAAGG  |
| CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA                |             |
| 101 GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATT TACACAGGAA  | GTGTGTCCTT  |
| CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA                |             |
|                                                            | XbaI        |
|                                                            | ~~~~~       |
| 151 ACAGCTATGA CCATGATTAC GAATTCTAG ACCCCCCCCC CGCATGCCAT  | SphI        |
| TGTCGATACT GGTAATAATG CTTAAAGATC TGGGGGGGGG GCGTACGGTA     | ~~~~~       |
|                                                            | HindIII     |
|                                                            | ~~~~~       |
| 201 AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA CCTGTGAAGT | PacI        |
| TTGAAGCATA TTACATGCCA TATGCTTCAA TATTCGAACT GGACACTTCA     |             |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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251 GAAAAATGGC GCAGATTGTG CGACATTTT TTTGCTGCC GTTTAATTAA
 CTTTTTACCG CGTCTAACAC GCTGTAAAAA AACAGACGG CAAATTAAAT

    ~~~~~
    FseI
    ~~~~~
301 GGGGGGGGC CGCCATTAT CAAAAAGGAT CTCAGAAGA TCCTTTGATC
 CCCCCCCCCG GCCGGTAATA GTTTTCCCTA GAGTTCTTCT AGGAAACTAG

351 TTTTCTACGG GGCTGACGC TCAGTGGAAC GAAACTCAC GTTAAGGGAT
 AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTGAGTG CAATTCCCTA

401 TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTAAATT
 AAACCAGTAC TCTAATAGTT TTTCCCTAGAA GTGGATCTAG GAAAAATTAA

451 AAAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
 TTTTACTTC AAAATTTAGT TAGATTTCAT ATATACTCAT TTGAACCAGA

501 GACAGTTACC CAATGCTTAA TCAGTGAGGC ACCTATCTCA GCGATCTGTC
 CTGTCAATGG GTTACGAATT AGTCACTCCG TGGATAGAGT CGCTAGACAG

551 TATTTCGTTC ATCCATAGTT GCCTGACTCC CCGTCGTGTA GATAACTACG
 ATAAAGCAAG TAGGTATCAA CGGACTGAGG GGCAGCACAT CTATTGATGC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |             |             |             |             |             |
|-----|-------------|-------------|-------------|-------------|-------------|
| 601 | ATACGGGAGG  | GCTTACCATC  | TGGCCCCCAGT | GCTGCAATGA  | TACCGCGAGA  |
|     | TATGCCCTCC  | CGAATGGTAG  | ACCGGGGTCA  | CGACGTTACT  | ATGGCGCTCT  |
| 651 | CCCACGCTCA  | CCGGCTCCAG  | ATTTATCAGC  | AATAAACCCAG | CCAGCCCGGAA |
|     | GGTGCGAGT   | GGCCGAGGTC  | TAAATAGTCG  | TTATTTGGTC  | GGTCGGCCCTT |
| 701 | GGGCCGAGCG  | CAGAAGTGGT  | CCTGCAACTT  | TATCCGCCCTC | CATCCAGTCT  |
|     | CCCGGCTCGC  | GTCCTCACCA  | GGACGTTGAA  | ATAGCGGGAG  | GTAGGTCAGA  |
| 751 | ATTAACTGTT  | GCCGGGAAGC  | TAGAGTAAGT  | AGTTCGCCCAG | TTAATAGTTT  |
|     | TAATTGACAA  | CGGCCCTTCG  | ATCTCATTC   | TCAAGCGGTC  | AATTATCAAA  |
| 801 | GCGCAACGTT  | GTTGCCATTG  | CTACAGGCAT  | CGTGGTGTCA  | CGCTCGTCGT  |
|     | CGCGTTGCAA  | CAACGGTAAC  | GATGTCCGTA  | GCACCCACAGT | GCGAGCAGCA  |
| 851 | TTGGTATGGC  | TTCAATTCAGC | TCCGGTTCCC  | AACGATCAAG  | GCGAGTTACA  |
|     | AACCATAACCG | AAGTAAGTCG  | AGGCCAAGGG  | TTGCTAGTTC  | CGCTCAATGT  |
| 901 | TGATCCCCCA  | TGTTGTGCAA  | AAAAGCGGTT  | AGCTCCTTCG  | GTCCCTCCGAT |
|     | ACTAGGGGGT  | ACAACACGTT  | TTTTTCGCCAA | TCGAGGGAAGC | CAGGAGGCTA  |
| 951 | CGTTGTCAGA  | AGTAAGTTGG  | CCGCAGTGTT  | ATCACTCATG  | GTTATGGCAG  |
|     | GCAACAGTCT  | TCATTCAACC  | GGCGTCACAA  | TAGTGAGTAC  | CAATACCGTC  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |             |             |            |             |
|------|-------------|-------------|-------------|------------|-------------|
| 1001 | CACTGCATAA  | TTCCTCTTACT | GTCATGCCCAT | CCGTAAGATG | CTTTTCTGTG  |
|      | GTGACCGTATT | AAGAGAAATGA | CAGTACGGTA  | GGCATTCTAC | GAAAGACAC   |
| 1051 | ACTGGTGAGT  | ACTCAACCAA  | GTCAATTCTGA | GAATAGTGTA | TGCGGCGACC  |
|      | TGACCACTCA  | TGAGTTGGTT  | CAGTAAGACT  | CTTATCACAT | ACGCCGCTGG  |
| 1101 | GAGTTGCTCT  | TGCCCGGCGT  | CAATACGGGA  | TAATACCGCG | CCACATAGCA  |
|      | CTCAACGAGA  | ACGGCCGCA   | GTTATGCCCT  | ATTATGGCGC | GGTGATATCGT |
|      |             |             | XmnI        |            |             |
|      |             |             | ~~~~~       |            |             |
| 1151 | GAACCTTAAA  | AGTGCTCATC  | ATTGGAAAC   | GTTCTTCGGG | GCGAAACTC   |
|      | CTTGAAATTT  | TCACGAGTAG  | TAACCTTTTG  | CAAGAAGCCC | CGCTTTTGAG  |
| 1201 | TCAAGGATCT  | TACCGCTGTT  | GAGATCCAGT  | TCGATGTAAC | CCACTCGCGC  |
|      | AGTTCCTAGA  | ATGGCGACAA  | CTCTAGGTCA  | AGCTACATTG | GGTGAGCGCG  |
| 1251 | ACCCAACGA   | TCCTCAGCAT  | CTTTTACTTT  | CACCAGCGTT | TCTGGGTGAG  |
|      | TGGGTGACT   | AGGAGTCGTA  | GAAATGAAA   | GTGTCGCAA  | AGACCCACTC  |
| 1301 | CAAAAACAGG  | AAGGCAAAAT  | GCCGCAAAA   | AGGGAATAAG | GCGACACGG   |
|      | GTTTTGTCC   | TTCCGTTTAA  | CGCGTTTTT   | TCCCTTATTC | CCGCTGTGCC  |
| 1351 | AAATGTTGAA  | TACTCATACT  | CTTCCTTTTT  | CAATATTATT | GAAGCATTTA  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            |            |             |             |             |
|------|------------|------------|-------------|-------------|-------------|
|      | TTTACAACTT | ATGAGTATGA | GAAGGAAAAA  | GTTATAATAA  | CTTCGTAAAT  |
|      |            |            |             | BsrGI       |             |
|      |            |            |             | ~~~~~       |             |
| 1401 | TCAGGGTTAT | TGTCTCATGA | GCGGATACAT  | ATTTGAATGT  | ACATGAAATT  |
|      | AGTCCCAATA | ACAGAGTACT | CGCCTATGTA  | TAAACTTACA  | TGTAATTAA   |
| 1451 | GTAACGTTA  | ATATTTTGT  | AAAATTCGCG  | TTAAATTTT   | GTTAAATCAG  |
|      | CATTGCAAT  | TATAAAACAA | TTTTAAGCGC  | AATTAAAAA   | CAATTTAGTC  |
| 1501 | CTCATTTTTT | AACCAATAGG | CCGAAATCGG  | CAAAATCCCT  | TATAAATCAA  |
|      | GAGTAAAAAA | TTGGTTATCC | GGCTTTAGCC  | GTTTTAGGGA  | ATATTTAGTT  |
| 1551 | AAGAATAGAC | CGAGATAGGG | TTGAGTGTTG  | TTCCAGTTTG  | GAACAAGAGT  |
|      | TTCTTATCTG | GCTCTATCCC | AACTCACAAAC | AAGGTCAAAC  | CTTGTTCTCA  |
| 1601 | CCACTATTAA | AGAACGTGGA | CTCCAACGTC  | AAAGGGCGAA  | AAACCGTCTA  |
|      | GGTGATAAAT | TCTTGCACTT | GAGGTTGCAG  | TTTCCCCGCTT | TTTGGCAGAT  |
| 1651 | TCAGGGCGAT | GGCCCACTAC | GAGAACCATC  | ACCCTAATCA  | AGTTTTTGG   |
|      | AGTCCCGCTA | CCGGTGATG  | CTCTTGGTAG  | TGGGATTAGT  | TCAAAAAAACC |

BanII  
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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |                                                                                                                   |
|------|-------------------------------------------------------------------------------------------------------------------|
| 1701 | GGTCGAGGTG CCGTAAAGCA CTAAATCGGA ACCCTAAAGG GAGCCCCCGA<br>CCAGCTCCAC GGCATTTCGT GATTAGCCT TGGGATTTCCT CTCGGGGGCT  |
| 1751 | TTTAGAGCTT GACGGGAA GCGCGCGAAC GTGGCGAGAA AGGAAGGGAA<br>AAATCTCGAA CTGCCCTTT CGGCCGCTTG CACCGCTCTT TCCTTCCCTT     |
| 1801 | GAAAGCGAAA GGAGCGGGCG CTAGGGCGCT GGCAAGTGTA GCGGTCACGC<br>CTTTCGCTTT CCTCGCCCGC GATCCCGCGA CCGTTCACAT CGCCAGTGCG  |
| 1851 | TGCGCGTAAC CACCACACCC GCCGCGCTTA ATGCGCCGCT ACAGGCGCG<br>ACGCGCATTG GTGGTGTTGG CGGCGCGAAT TACGCGGCGA TGTCCCGCGC   |
| 1901 | TGCTAGCGGA GTGTATACTG GCTTACTATG TTGGCACTGA TGAGGGTGTC<br>ACGATCGCCT CACATATGAC CGAATGATAC AACCGTGACT ACTCCCACAG  |
| 1951 | AGTGAAGTGC TTCATGTGGC AGGAGAAAA AGGCTGCACC GGTGCGTCAG<br>TCACTTCACG AAGTACACCG TCCTCTTTT TCCGACGTGG CCACGCAGTC    |
| 2001 | CAGAATATGT GATACAGGAT ATATTCCGCT TCCTCGCTCA CTGACTCGCT<br>GTCCTTATACA CTATGTCCCTA TATAAGCGA AGGAGCGAGT GACTGAGCGA |

NheI

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XmnI

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AgeI

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|               |             |            |            |            |             |
|---------------|-------------|------------|------------|------------|-------------|
| 2051          | ACGCTCGGTC  | GTTCGACTGC | GGCGAGCGGA | AATGGCTTAC | GAACGGGGCG  |
|               | TGCGAGCCAG  | CAAGCTGACG | CCGCTCGCCT | TTACCGAATG | CTTGCCCCCGC |
| 2101          | GAGATTTCCT  | GGAAGATGCC | AGGAAGATAC | TTAACAGGGA | AGTGAGAGGG  |
|               | CTCTAAAGGA  | CCTTCTACGG | TCCTTCTATG | AATTGTCCCT | TCACTCTCCC  |
| 2151          | CCGCGGCAAA  | GCCGTTTTC  | CATAGGCTCC | GCCCCCCTGA | CAAGCATCAC  |
|               | GGCGCCGTTT  | CGGCAAAAAG | GTATCCGAGG | CGGGGGGACT | GTTTCGTAGTG |
| 2201          | GAAATCTGAC  | GCTCAAATCA | GTGGTGGCGA | AACCCGACAG | GACTATAAAG  |
|               | CTTTAGACTG  | CGAGTTTAGT | CACCACCGCT | TTGGGCTGTC | CTGATATTTC  |
| 2251          | ATACCAGGCG  | TTTCCCCCTG | GCGGCTCCCT | CCTGCGCTCT | CCTGTTCCCTG |
|               | TATGGTCCCG  | AAAGGGGGAC | CGCCGAGGGA | GGACGCGAGA | GGACAAGGAC  |
| AgeI<br>~~~~~ |             |            |            |            |             |
| 2301          | CCTTTCGGTT  | TACCGGTGTC | ATCCGCTGT  | TATGGCCGCG | TTTGTCTCAT  |
|               | GGAAGCCAA   | ATGCCACACG | TAAGGCGACA | ATACCGGCGC | AAACAGAGTA  |
| 2351          | TCCACGCCCTG | ACACTCAGTT | CCGGGTAGGC | AGTTCGCTCC | AAGCTGGACT  |
|               | AGGTGCGGAC  | TGTGAGTCAA | GGCCCATCCG | TCAAGCGAGG | TTCGACCCTGA |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------|
| 2401  | GTATGCACGA ACCCCCCGTT CAGTCCGACC GCTGCGCCTT ATCCGGTAAC<br>CATACGTGCT TGGGGGGCAA GTCAGGCTGG CGACGCGGAA TAGGCCATTG  |
| 2451  | TATCGTCTTG AGTCCAACCC GGAAAGACAT GCAAAAGCAC CACTGGCAGC<br>ATAGCAGAAC TCAGGTTGGG CCTTTCCTGTA CGTTTTCGTG GTGACCGTCG |
| 2501  | AGCCACTGGT AATTGATTGA GAGGAGTTAG TCTTGAAGTC ATGCGCCGGT<br>TCGGTGACCA TTAACATAAT CTCCTCAATC AGAACTTCAG TACGCGGCCA  |
| 2551  | TAAGGCTAAA CTGAAAGGAC AAGTTTTAGT GACTGCGCTC CTCCAAGCCA<br>ATTCCGATT GACTTTCCTG TTCAAAATCA CTGACGCGAG GAGGTTCCGT   |
| 2601  | GTTACCTCGG TTCAAAGAGT TGGTAGCTCA GAGAACCTAC GAAAACCCG<br>CAATGGAGCC AAGTTTCTCA ACCATCGAGT CTCTTGGATG CTTTTTGGCG   |
| 2651  | CCTGCAAGGC GGTTTTCG TTTTCAGAGC AAGAGATTAC GCGCAGACCA<br>GGACGTTCCG CCAAAAGC AAAAGTCTCG TTCTCTAATG CGCGTCTGGT      |
| BglII |                                                                                                                   |
| 2701  | AAACGATCTC AAGAAGATCA TCTTATTA<br>TTTGCTAGAG TTCTTCTAGT AGAATAAT                                                  |

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Figure 35b: List of oligonucleotides used for synthesis of modules

M1: PCR using template

NoVspAatII: TAGACGTC

M2: synthesis

BloxA-A: TATGAGATCTCATAACTTCGTATAATGTACGCTATACG-  
AAGTTAT

BloxA-B: TAATAACTTCGTATAGCATAACATTATACGAAGTTATG-  
AGATCTCA

M3: PCR, NoVspAatII as second oligo

XloxS-muta: CATTTTTGCCCTCGTTATCTACGCATGCGATAACTTCGTA-  
TAGCGTACATTATACGAAGTTATTCTAGACATGGTCATAGCTGTTTCCTG

M7-I: PCR

gIIIINEW-fow: GGGGGGAATTCGGTGGTGGTGGATCTGCGTGCGCTG-  
AAACGGTTGAAAGTTG

gIIIINEW-rev: CCCCCCAAGCTTATCAAGACTCCTTATTACG

M7-II: PCR

gIIIss-fow: GGGGGGGGAATTCGGAGGCGGTCCGGTGGTGGC

M7-III: PCR

gIIIsupernew-fow: GGGGGGGGAATTCGAGCAGAAGCTGATCTCT-  
GAGGAGGATCTGTAGGGTGGTGGCTCTGGTTCCGGTGATTTG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M8: synthesis

lox514-A: CCATAACTTCGTATAATGTACGCTATACGAAGTTATA

lox514-B: AGCTTATAACTTCGTATAGCGTACATTATACGAAGT-  
TATGGCATG

M9II: synthesis

M9II-fow: AGCTTGACCTGTGAAGTGAAAAATGGCGCAGATT-  
GTGCGACATTTTTTTTGTCTGCCGTTTAATTAAAGGGGGGGT

M9II-rev: GTACACCCCCCCCCAGGCCGGCCCCCCCCCCCCCTTAA-  
TTAAACGGCAGACAAAAAAAATGTCGCACAATCTGCG

M10II: assembly PCR with template

bla-fow: GGGGGGGTGTACATTCAAATATGTATCCGCTCATG

bla-seq4: GGGTTACATCGAACTGGATCTC

bla1-muta: CCAGTTCGATGTAACCCACTCGCGCACCCAACTGATC-  
CTCAGCATCTTTACTTTCACC

blaII-muta: ACTCTAGCTTCCCGGCAACAGTTAATAGACTGGATG-  
GAGGCGG

bla-NEW: CTGTTGCCGGGAAGCTAGAGTAAG

bla-rev: CCCCCCTTAATTAAGGGGGGGGGCCGGCCATTATCAAA-  
AAGGATCTCAAGAAGATCC

M11II/III: PCR, site-directed mutagenesis

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

f1-fow: GGGGGGGGCTAGCACGCGCCCTGTAGCGGCGCATTA

f1-rev: CCCCCCTGTACATGAAATTGTAAACGTTAATATTTG

f1-t133.muta: GGGCGATGGCCCACTACGAGAACCATCACCTAATC

M12: assembly PCR using template

p15-fow: GGGGGGAGATCTAATAAGATGATCTTCTTGAG

p15-NEWI: GAGTTGGTAGCTCAGAGAACCTACGAAAAACCGCCCTG-  
CAAGGCG

p15-NEWII: GTAGGTTCTCTGAGCTACCAACTC

p15-NEWIII: GTTCCCCCTGGCGGCTCCCTCCTGCGCTCTCCTGTTCT-  
GCC

p15-NEWIV: AGGAGGGAGCCGCCAGGGGGGAAAC

p15-rev: GACATCAGCGCTAGCGGAGTGTATAC

M13: synthesis

BloxXB-A: GATCTCATAACTTCGTATAATGTATGCTATACGAAGTTA-  
TTCA

BloxXB-B: GATCTGAATAACTTCGTATAGCATACATTATACGAAGTTA-  
TGAGA

M14-Ext2: PCR, site-directed mutagenesis

ColEXT2-fow: GGGGGGGGAGATCTGACCAAATCCCTTAACGTGAG

Col-mutal: GGTATCTGCGCTCTGCTGTAGCCAGTTACCTTCGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

Col-rev: CCCCCCGCTAGCCATGTGAGCAAAGGCCAGCAA

M17: assembly PCR using template

CAT-1: GGGACGTCGGGTGAGGTTCCAAC

CAT-2: CCATACGGAACCTCCGGGTGAGCATTATC

CAT-3: CCGGAGTTCCGTATGG

CAT-4: ACGTTTAAATCAAACTGG

CAT-5: CCAGTTTTGATTTAAACGTAGCCAATATGGACAACCTCTTC-  
GCCCCCGTTTTCACTATGGGCAAATATT

CAT-6: GGAAGATCTAGCACCAGGCGTTTAAG

M41: assembly PCR using template

LAC1: GAGGCCGGCCATCGAATGGCGCAAAAC

LAC2: CGCGTACCGTCCTCATGGGAGAAAATAATAC

LAC3: CCATGAGGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCA-  
TTGGGTCACCAGCAAATCCGCTGTTAGCTGGCCCATTAAG

LAC4: GTCAGCGGCGGGATATAACATGAGCTGTCCTCGGTATCGTCG

LAC5: GTTATATCCCGCCGCTGACCACCATCAAAC

LAC6: CATCAGTGAATCGGCCAACGCGCGGGGAGAGGCGGTTTTCGT4TTG-  
GGAGCCAGGGTGGTTTTTC

LAC7: GGTTAATTAACCTCACTGCCCCGCTTCCAGTCGGGAAACCTGTCGTGCC-  
AGCTGCATCAGTGAATCGGCCAAC

M41-MCS-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTT-  
AAGGGGGGGGGGGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M41-MCS-rev: CTAGCCCCCCCCCCCCCTTAAGCCCCCCCCCGGTCCGGT-TTAAACACTAGT

M41-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTTAA-GGGGGGGGGGGG

M41-rev: CCCCCCTTAAGTGGGCTGCAAAACAAAACGGCCTCC-TGTCAGGAAGCCGCTTTTATCGGGTAGCCTCACTGCCCGCTTCC

M41-A2: GTTGTTGTGCCACGCGGTTAGGAATGTAATTCAGCTCCGC

M41-B1: AACCGCGTGGCACAACAAC

M41-B2: CTTGTTCTACCATCGACACGACCACGCTGGCACCCAGTTG

M41-C1: GTGTCGATGGTAGAACGAAG

M41-CII: CCACAGCAATAGCATCCTGGTCATCCAGCGGATAGTT-AATAATCAGCCCACTGACACGTTGCGCGAG

M41-DI: GACCAGGATGCTATTGCTGTGG

M41-DII: CAGCGCGATTGCTGGTGGCCCAATGCGACCAGATGC

M41-EI: CACCAGCAAATCGCGCTG

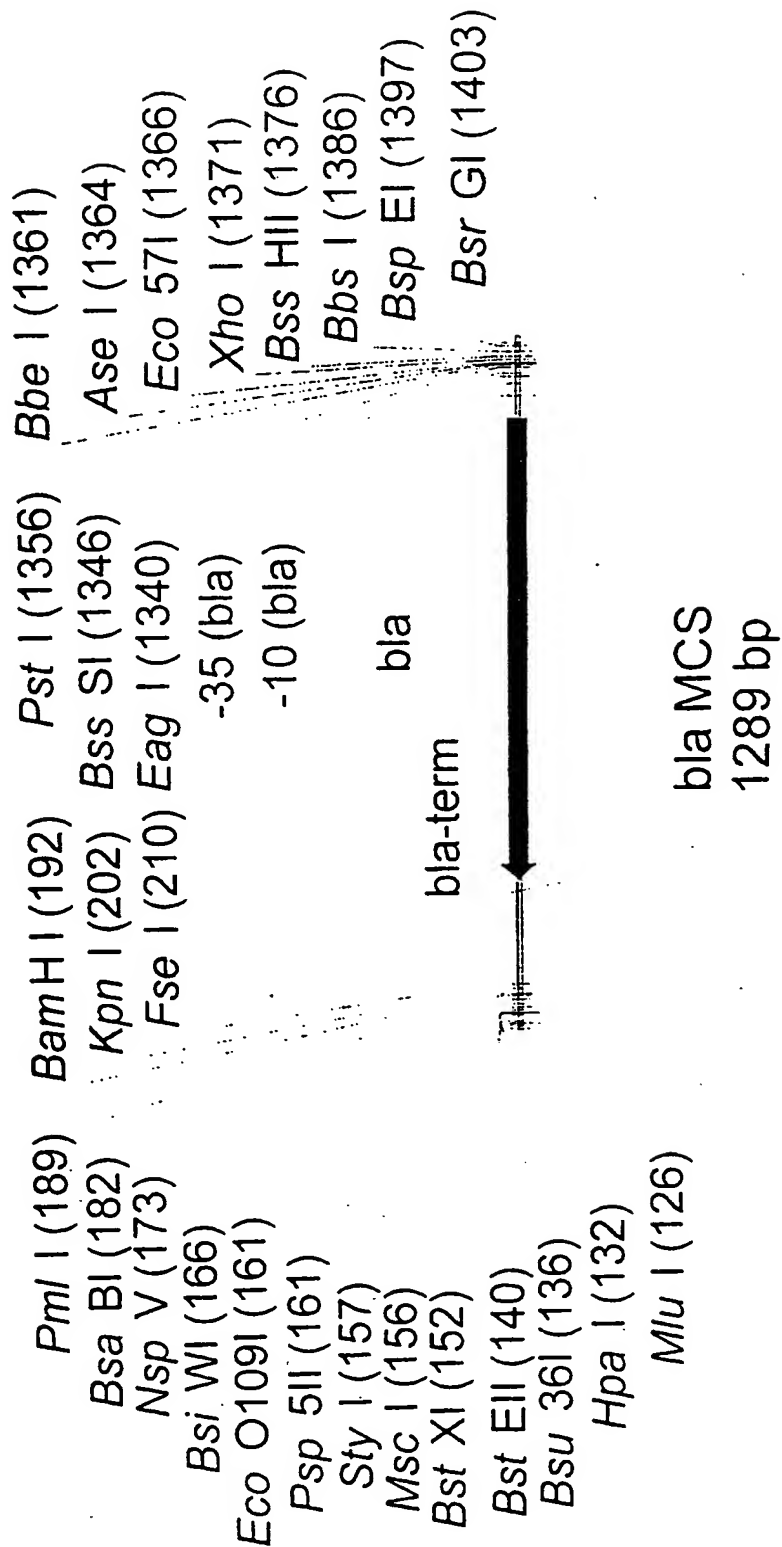
M41-EII: CCCGGACTCGGTAATGGCACGCATTGCGCCCAGCGCC

M41-FI: GCCATTACCGAGTCCGGG

M42: synthesis

Eco-H5-Hind-fow: AATCCACCATCATCACCATTGACGTCTA

Eco-H5-Hind-rev: AGCTTAGACGTCAATGGTGATGATGGTGG

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module

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# styI

Psp5II

Eco0109I

# BstXI

MluI Bsu36I

MSCI

BsiWI NspV

# BstEII

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189 / 204

Pm1 I

Is

KpnI

# BamHI

NspVBsaBI

176 AGATTACCAT CACGTGGATC CGGTACCAGG CCGGCCATTA TCAAAAAGGA  
TCTAATGGTA GTGCACCTAG GCCATGGTCC GGCCGGTAAT AGTTTTCCT

226 TCTCAAGAAG ATCCCTTTGAT CTTTCTACG GGTCTGACG CTCAGTGGAA  
AGAGTTCTTC TAGGAAACTA GAAAGATGC CCCAGACTGC GAGTCACCTT

276 CGAAACTCA CGTTAAGGA TTTTGGTCAT GAGATTATCA AAAAGGATCT  
GCTTTTGAGT GCAATTCCCT AAAACCAAGTA CTCTAATAGT TTTTCCTAGA

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|     |                           |                           |                           |                           |                           |
|-----|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| 326 | TCACCTAGAT<br>AGTGGATCTA  | CCTTTTAAAT<br>GGAAAATTTA  | TAAAAATGAA<br>ATTTTACTT   | GTTTAAATC<br>CAAAATTAG    | AATCTAAAGT<br>TTAGATTTC   |
| 376 | ATATATGAGT<br>TATATACTCA  | AAACTTGGTC<br>TTTGAACCCAG | TGACAGTTAC<br>ACTGTCAATG  | CAATGCTTAA<br>GTTACGAAAT  | TCAGTGAGGC<br>AGTCACTCCG  |
| 426 | ACCTATCTCA<br>TGGATAGAGT  | GCGATCTGTC<br>CGCTAGACAG  | TATTCGTTC<br>ATAAAGCAAG   | ATCCATAGTT<br>TAGGTATCAA  | GCCTGACTCC<br>CGGACTGAGG  |
| 476 | CCGTCGTGTA<br>GGCAGCACAT  | GATAACTACG<br>CTATTGATGC  | ATACGGGAGG<br>TATGCCCTCC  | GCTTACCATC<br>CGAATGGTAG  | TGGCCCCAGT<br>ACCGGGGTCA  |
| 526 | GCTGCAATGA<br>CGACGTTACT  | TACCGCGAGA<br>ATGGCGCTCT  | CCCACGCTCA<br>GGTGCGAGT   | CCGGCTCCAG<br>GGCCGAGGTC  | ATTATCAGC<br>TAAATAGTCG   |
| 576 | AATAAACCCAG<br>TTATTGGTC  | CCAGCCGGAA<br>GGTCGGCCTT  | GGCCCGAGCG<br>CCC GGCTCGC | CAGAA GTGGT<br>GTCTTCACCA | CCTGCAACTT<br>GGACGTTGAA  |
| 626 | TATCCGCCCTC<br>ATAGGCGGAG | CATCCAGTCT<br>GTAGGTCAGA  | ATTAAGTGT<br>TAATTGACAA   | GCCGGGAAGC<br>CGGCCCTTCG  | TAGAGTAAGT<br>ATCTCATTTCA |
| 676 | AGTTCGCCCAG<br>TCAAGCGGTC | TTAATAGTTT<br>AATTATCAAA  | GCGCAACGTT<br>CGCGTTGCAA  | GTTGCCATTG<br>CAACGGTAAC  | CTACAGGCAT<br>GATGTCCGTA  |



Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|      |             |             |              |             |             |
|------|-------------|-------------|--------------|-------------|-------------|
| 726  | CGTGGTGTCA  | CGCTCGTCGT  | TTGGTATGGC   | TTCATTCAGC  | TCCGGTTCCC  |
|      | GCACCAACAGT | GCGAGCAGCA  | AACCATACCG   | AAGTAAGTCG  | AGGCCAAGGG  |
| 776  | AACGATCAAG  | GCGAGTTACA  | TGATCCCCCA   | TGTTGTGCAA  | AAAAGCGGTT  |
|      | TTGCTAGTTC  | CGCTCAATGT  | ACTAGGGGGT   | ACAACACGTT  | TTTTTCGCCAA |
| 826  | AGCTCCTTCG  | GTCCCTCCGAT | CGTTGTCAGA   | AGTAAGTTGG  | CCGCAGTGTT  |
|      | TCGAGGAAGC  | CAGGAGGCTA  | GCAACAGTCT   | TCATTCAACC  | GGGTCACAA   |
| 876  | ATCACTCATG  | GTTATGGCAG  | CAC TG CATAA | TTC TCTTACT | GTCATGCCAT  |
|      | TAGTGAGTAC  | CAATACCGTC  | GTGACGTATT   | AAGAGAAATGA | CAGTACGGTA  |
| 926  | CCGTAAGATG  | CTTTTCTGTG  | ACTGGTGAGT   | ACTCAACCAA  | GTCATTCTGA  |
|      | GGCATTCTAC  | GAAAAGACAC  | TGACCACTCA   | TGAGTTGGTT  | CAGTAAGACT  |
| 976  | GAATAGTGTA  | TGCGGCGACC  | GAGTTGCTCT   | TGCCCCGGCGT | CAATACGGGA  |
|      | CTTATCACAT  | ACGCCGCTGG  | CTCAACGAGA   | ACGGGCCGCA  | GTTATGCCCT  |
| 1026 | TAATACCGCG  | CCACATAGCA  | GAAC TTTAAA  | AGTGCTCATC  | ATTGGAA AAC |
|      | ATTATGGCGC  | GGTGATATCGT | CTTGAAAATT   | TCACGAGTAG  | TAACTTTTG   |
| 1076 | GTTCTTCGGG  | GCGAAAAC TC | TCAAGGATCT   | TACCGCTGTT  | GAGATCCAGT  |
|      | CAAGAAGCCC  | CGCTTTTGAG  | AGTTCCTAGA   | ATGGCGACAA  | CTCTAGGTCA  |

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Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|      |            |            |             |            |            |
|------|------------|------------|-------------|------------|------------|
| 1126 | TCGATGTAAC | CCACTCGTGC | ACCCAACCTGA | TCTTCAGCAT | CTTTTACTTT |
|      | AGCTACATTG | GGTGAGCACG | TGGGTTGACT  | AGAAGTCGTA | GAAAATGAAA |
|      |            | BSSI       |             | Eco57I     |            |
|      |            | ~~~~~      |             | ~~~~~      |            |
| 1176 | CACCAGCGTT | TCTGGGTGAG | CAAAACACAGG | AAGGCAAAAT | GCCGCAAAA  |
|      | GTGGTCGCAA | AGACCCACTC | GTTTTTGTCC  | TTCCGTTTTA | CGCGTTT    |
| 1226 | AGGGAATAAG | GGCGACACGG | AAATGTTGAA  | TACTCATACT | CTTCCTTTT  |
|      | TCCCTTATTC | CCGCTGTGCC | TTTACAACCTT | ATGAGTATGA | GAAGGAAAA  |
| 1276 | CAATATTATT | GAAGCATTTA | TCAGGGTTAT  | TGTCTCATGA | GCGGATACAT |
|      | GTTATAATAA | CTTCGTAAAT | AGTCCCAATA  | ACAGAGTACT | CGCCTATGTA |
|      |            |            | PstI        |            | XhoI       |
|      |            |            | ~~~~~       |            | ~~~~~      |
|      |            | EagI       | BSSI        | BbeI       | AseI       |
|      |            | ~~~~~      | ~~~~~       | ~~~~~      | ~~~~~      |
| 1326 | ATTGAAATGT | ACTCGGCCGC | ACGAGCTGCA  | GCGGCCATTA | ATGGCTCGAG |
|      | TAAACTTACA | TGAGCCGGCG | TGCTCGACGT  | CCGCGGTAAT | TACCGAGCTC |
|      |            |            |             |            |            |
|      | BssHII     |            | BspEI       | BsrGI      |            |
|      | ~~~~~      |            | ~~~~~       | ~~~~~      |            |

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|      |            |            |            |           |
|------|------------|------------|------------|-----------|
| 1376 | CGCGCTTCAG | CGCTTTGTCT | TCCGGATGTA | CATGAAATT |
|      | GCGCGAAGTC | GCGAAACAGA | AGGCCTACAT | GTACTTTAA |
|      | Eco57I     | BbsI       |            |           |
|      | ~~~~~      | ~~~~~      |            |           |

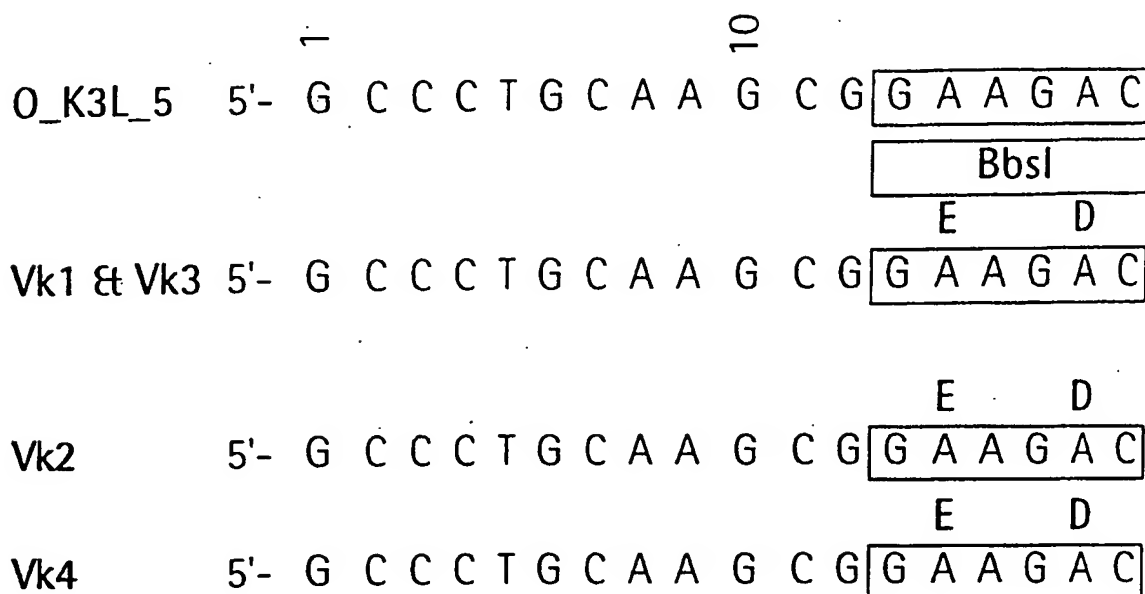
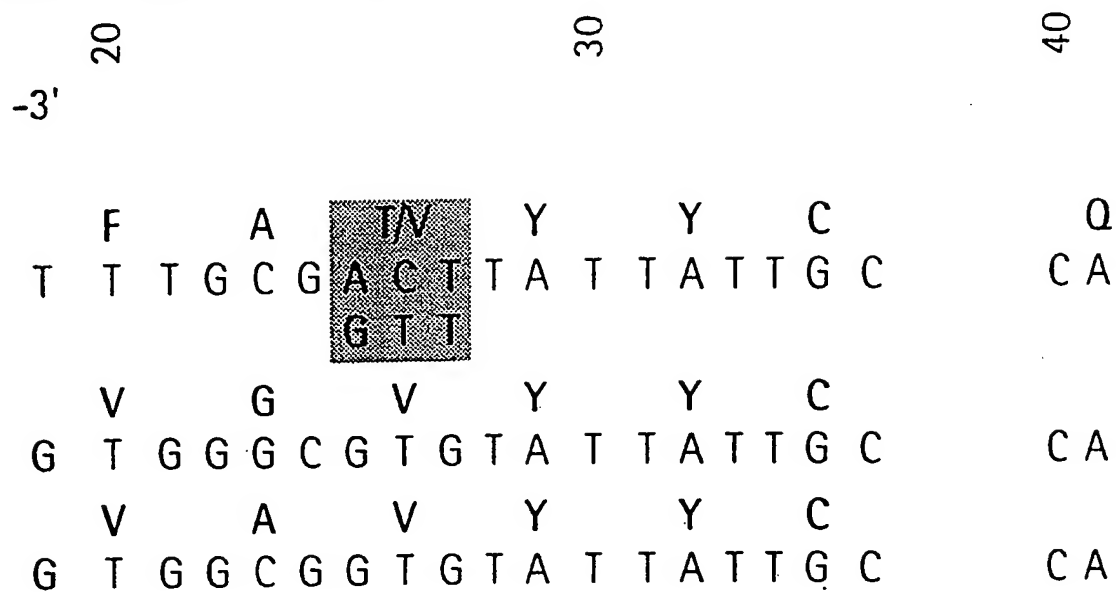
Figure 37: Oligo and primer design for V $\kappa$  CDR3 libraries

Figure 37: Oligo and primer design for V $\kappa$  CDR3 libraries

|   |       |
|---|-------|
| A |       |
| C |       |
| D |       |
| E |       |
| F | T T T |
| G |       |
| H | C A T |
| I |       |
| K |       |
| L | C T T |
| M | A T G |
| N |       |
| P |       |
| Q | C A G |
| R |       |
| S |       |
| T |       |
| V |       |
| W |       |
| Y |       |

80% Q











Figure 38: Oligo and primer design for V $\lambda$  CDR3 libraries

|   |    |    |    |     |   |   |   |     |    |   |   |   |   |    |    |   |   |   |   |   |   |   |  |  |  |  |  |
|---|----|----|----|-----|---|---|---|-----|----|---|---|---|---|----|----|---|---|---|---|---|---|---|--|--|--|--|--|
|   |    |    |    | 60  |   |   |   |     | 70 |   |   |   |   | 80 |    |   |   |   |   |   |   |   |  |  |  |  |  |
|   |    |    |    |     |   |   |   | G   | G  | G | T | K | L |    |    |   |   |   |   |   |   |   |  |  |  |  |  |
|   |    |    |    |     |   |   |   | G   | G  | C | G | G | C | A  | C  | G | A | A | G | T | T | A |  |  |  |  |  |
| - | G  | C  | T  | gap | G | C | T | gap | G  | C | T | G | C | T  |    |   |   |   |   |   |   |   |  |  |  |  |  |
|   | G  | A  | T  | G   | A | T | G | A   | T  | G | A | T | G | A  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | G  | A  | G  | G   | A | G | G | A   | G  | G | A | G | G | A  | G  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | T  | T  | T  | T   | T | T | T | T   | T  | T | T | T | T | T  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | G  | G  | T  | G   | G | T | G | G   | T  | G | G | T | G | G  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | C  | A  | T  | C   | A | T | C | A   | T  | C | A | T | C | A  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | A  | T  | T  | A   | T | T | A | T   | T  | A | T | T | A | T  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | A  | A  | G  | A   | A | G | A | A   | G  | A | A | G | A | A  | G  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | C  | T  | T  | C   | T | T | C | T   | T  | C | T | T | C | T  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | A  | T  | G  | A   | T | G | A | T   | G  | A | T | G | A | T  | G  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | A  | A  | T  | A   | A | T | A | A   | T  | A | A | T | A | A  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | C  | C  | T  | C   | C | T | C | C   | T  | C | C | T | C | C  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | C  | A  | G  | C   | A | G | C | A   | G  | C | A | G | C | A  | G  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | C  | G  | T  | C   | G | T | C | G   | T  | C | G | T | C | G  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | T  | C  | T  | T   | C | T | T | C   | T  | T | C | T | T | C  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | A  | C  | T  | A   | C | T | A | C   | T  | A | C | T | A | C  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | G  | T  | T  | G   | T | T | G | T   | T  | G | T | T | G | T  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   |    |    |    |     |   |   |   |     |    |   |   |   |   |    | T  | G | G |   |   |   |   |   |  |  |  |  |  |
|   | T  | A  | T  | T   | A | T | T | A   | T  | T | A | T | T | A  | T  |   |   |   |   |   |   |   |  |  |  |  |  |
|   | 18 |    |    |     |   |   |   |     |    |   |   |   |   |    | 19 |   |   |   |   |   |   |   |  |  |  |  |  |
|   | 18 | 18 |    |     |   |   |   |     |    |   |   |   |   |    | 19 |   |   |   |   |   |   |   |  |  |  |  |  |
|   | 18 | 18 | 18 |     |   |   |   |     |    |   |   |   |   |    | 19 |   |   |   |   |   |   |   |  |  |  |  |  |

Variability

3.32E+05

5.98E+06

1.08E+08

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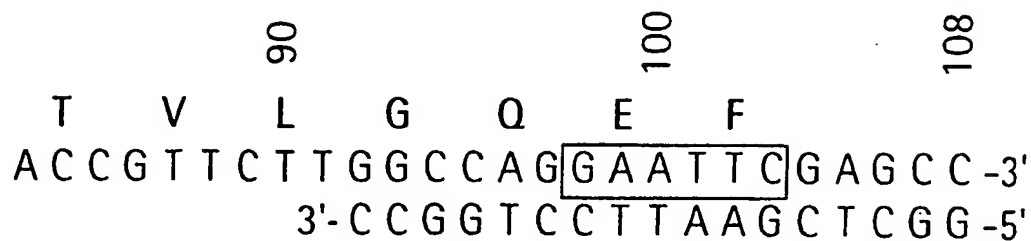
Figure 38: Oligo and primer design for V $\lambda$  CDR3 libraries

Figure 39: functional map of expression vector series pBS13

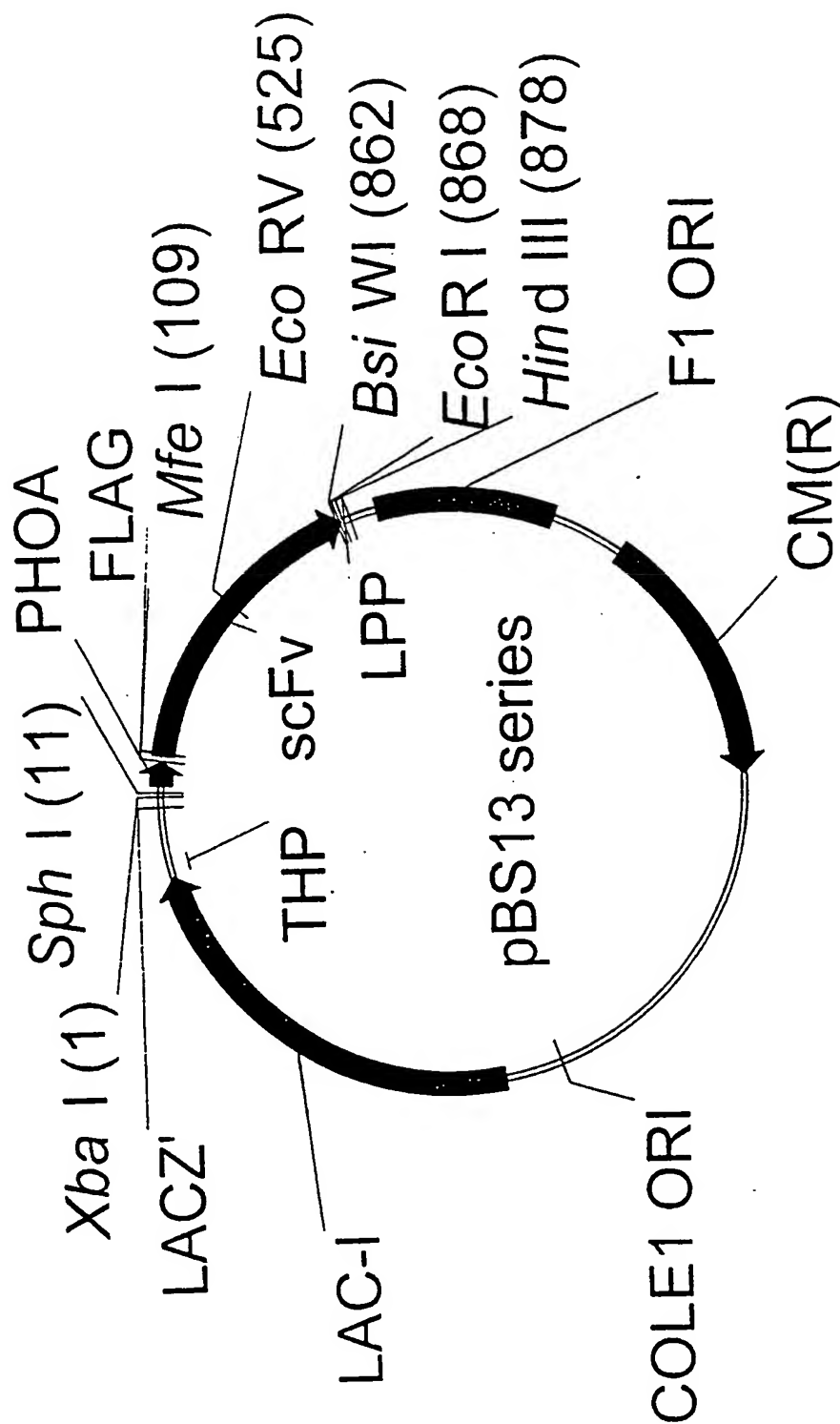


Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

| % soluble | $\kappa 1$ | $\kappa 2$ | $\kappa 3$ | $\kappa 4$ | $\lambda 1$ | $\lambda 2$ | $\lambda 3$ |
|-----------|------------|------------|------------|------------|-------------|-------------|-------------|
| H1A       | 61%        | 58%        | 52%        | 42%        | 90%         | 61%         | 60%         |
| H1B       | 39%        | 48%        | 66%        | 48%        | 47%         | 39%         | 36%         |
| H2        | 47%        | 57%        | 46%        | 49%        | 37%         | 36%         | 45%         |
| H3        | 85%        | 67%        | 76%        | 61%        | 80%         | 71%         | 83%         |
| H4        | 69%        | 52%        | 51%        | 44%        | 45%         | 33%         | 42%         |
| H5        | 49%        | 49%        | 46%        | 67%        | 54%         | 46%         | 47%         |
| H6        | 90%        | 58%        | 54%        | 47%        | 45%         | 50%         | 51%         |

| Total amount<br>compared to H3 $\kappa 2$ | $\kappa 1$ | $\kappa 2$ | $\kappa 3$ | $\kappa 4$ | $\lambda 1$ | $\lambda 2$ | $\lambda 3$ |
|-------------------------------------------|------------|------------|------------|------------|-------------|-------------|-------------|
| H1A                                       | 289%       | 94%        | 166%       | 272%       | 20%         | 150%        | 78%         |
| H1B                                       | 219%       | 122%       | 89%        | 139%       | 117%        | 158%        | 101%        |
| H2                                        | 186%       | 223%       | 208%       | 182%       | 126%        | 60%         | 97%         |
| H3                                        | 50%        |            | 71%        | 54%        | 59%         | 130%        | 47%         |
| H4                                        | 37%        | 55%        | 60%        | 77%        | 195%        | 107%        | 251%        |
| H5                                        | 98%        | 201%       | 167%       | 83%        | 93%         | 128%        | 115%        |
| H6                                        | 65%        | 117%       | 89%        | 109%       | 299%        | 215%        | 278%        |

Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

| Soluble amount<br>compared to H3κ2 | κ1   | κ2   | κ3   | κ4   | λ1   | λ2   | λ3   |
|------------------------------------|------|------|------|------|------|------|------|
| H1A                                | 191% | 88%  | 121% | 122% | 26%  | 211% | 76%  |
| H1B                                | 124% | 95%  | 83%  | 107% | 79%  | 142% | 59%  |
| H2                                 | 126% | 204% | 139% | 130% | 66%  | 50%  | 70%  |
| H3                                 | 63%  | -    | 81%  | 49%  | 69%  | 143% | 61%  |
| H4                                 | 40%  | 47%  | 49%  | 54%  | 95%  | 55%  | 125% |
| H5                                 | 69%  | 158% | 116% | 80%  | 72%  | 84%  | 84%  |
| H6                                 | 85%  | 122% | 87%  | 77%  | 162% | 162% | 212% |
|                                    | McPC |      |      |      |      |      |      |
| soluble                            | 38%  |      |      |      |      |      |      |
| %H3κ2 total                        | 117% |      |      |      |      |      |      |
| %H3κ2 soluble                      | 69%  |      |      |      |      |      |      |

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/03647

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/13 C12N15/10 C12N15/62 C12N15/70 C12N1/21  
C07K1/04 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
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☒ Further documents are listed in the continuation of box C.

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- "A" document member of the same patent family

Date of the actual completion of the international search

30 January 1997

Date of mailing of the international search report

11.02.97

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## INTERNATIONAL SEARCH REPORT

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                       |                       |
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## INTERNATIONAL SEARCH REPORT

Int. Patent Application No

PCT/EP 96/03647

| C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |
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| Category *                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                             | Relevant to claim No. |
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| A                                                   | <p>WO 95 11998 A (UNITED BIOMEDICAL INC) 4<br/>May 1995<br/>see the whole document<br/>---</p>                                                                                                                                                                                                                                                                                                                                                 | 1-55                  |
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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|                                           |                     | DE-T- 68913658             | 08-09-94            |
|                                           |                     | ES-T- 2052027              | 01-07-94            |
|                                           |                     | WO-A- 9005144              | 17-05-90            |
|                                           |                     | JP-T- 3502801              | 27-06-91            |
| -----                                     |                     |                            |                     |
| WO-A-9511998                              | 04-05-95            | AU-A- 8091694              | 22-05-95            |
|                                           |                     | EP-A- 0725838              | 14-08-96            |
| -----                                     |                     |                            |                     |